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(54) Title: ARYL SULFONAMIDE AND SULFAMIDE DERIVATIVES AND USES THEREOF		
(57) Abstract This invention is directed to novel aryl sulfonamide and sulfamide compounds which bind selectively to and inhibit the activity of the human Y5 receptor. This invention is also related to uses of these compounds for the treatment of feeding disorders such as obesity, anorexia nervosa, bulimia nervosa, and abnormal conditions such as sexual/reproductive disorders, depression, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure or sleep disturbances and for the treatment of any disease in which antagonism of a Y5 receptor may be useful.		

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**Aryl Sulfonamide and Sulfamide Derivatives**  
**and Uses Thereof**

Throughout this application, various references are referred to within parentheses. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains. Full bibliographic citation for these references may be found at the end of this application, preceding the sequence listing and the claims.

**Background of the Invention**

The peptide neurotransmitter neuropeptide Y (NPY) is a 36 amino acid member of the pancreatic polypeptide family with widespread distribution throughout the mammalian nervous system (Dumont et al., 1992). The family includes the namesake pancreatic polypeptide (PP), synthesized primarily by endocrine cells in the pancreas; peptide YY (PYY), synthesized primarily by endocrine cells in the gut; and NPY, synthesized primarily in neurons (Michel, 1991; Dumont et al., 1992; Wahlestedt and Reis, 1993). All pancreatic polypeptide family members share a compact structure involving a "PP-fold" and a conserved C-terminal hexapeptide ending in Tyr<sup>36</sup> (or Y<sup>36</sup> in the single letter code). The striking conservation of Y<sup>36</sup> has prompted the reference to the pancreatic polypeptides' receptors as "Y-type" receptors (Wahlestedt et al., 1987), all of which are proposed to function as seven transmembrane-spanning G protein-coupled receptors (Dumont et al., 1992).

NPY and its relatives elicit a broad range of physiological effects through activation of at least five G protein-coupled receptor subtypes known as Y1, Y2, Y3, Y4 (or PP), and the "atypical Y1". While the Y1, Y2, Y3, and Y4 (or PP) receptors were each described previously in

both radioligand binding and functional assays, the "atypical Y1" receptor is unique in that its classification is based solely on feeding behavior induced by various peptides including NPY.

5 The role of NPY in normal and abnormal eating behavior, and the ability to interfere with NPY-dependent pathways as a means to appetite and weight control, are areas of great interest in pharmacological and pharmaceutical  
10 research (Sahu and Kalra, 1993; Dryden et al., 1994). NPY is considered to be the most powerful stimulant of feeding behavior yet described (Clark et al., 1984; Levine and Morley, 1984; Stanley and Leibowitz, 1984). The stimulation of feeding behavior by NPY is thought to occur  
15 primarily through activation of the hypothalamic "atypical Y1" receptor. For example, direct injection of NPY into the hypothalamus of satiated rats can increase food intake up to 10-fold over a 4-hour period (Stanley et al., 1992). Similar studies using other peptides has resulted in a  
20 pharmacologic profile for the "atypical Y1" receptor according to the rank order of potencies of peptides in stimulating feeding behavior as follows:  $NPY_{2-36} \geq NPY \sim PYY \sim [Leu^{31}, Pro^{34}]NPY > NPY_{13-36}$  (Kalra et al., 1991; Stanley et al., 1992). The profile is similar to that of  
25 a Y1-like receptor except for the anomalous ability of  $NPY_{2-36}$  to stimulate food intake with potency equivalent or better than that of NPY. A subsequent report in J. Med. Chem. by Balasubramaniam and co-workers (1994) showed that feeding can be regulated by  $[D-Trp^{32}]NPY$ . While this  
30 peptide was presented as an NPY antagonist, the published data at least in part support a stimulatory effect of  $[D-Trp^{32}]NPY$  on feeding. In contrast to other NPY receptor subtypes, the "feeding" receptor has never been characterized for peptide binding affinity in radioligand  
35 binding assays. The fact that a single receptor could be

responsible for the feeding response has been impossible to validate in the absence of an isolated receptor protein; the possibility exists, for example, that the feeding response could be a composite profile of Y1 and Y2 subtypes.

This problem has been addressed by cloning rat and human cDNAs which encode a single receptor protein, referred to herein as Y5, whose pharmacologic profile links it to the "atypical Y1" receptor. The identification and characterization by applicants of a single molecular entity which explains the "atypical Y1" receptor allows the design of selective drugs which modulate feeding behavior. It is important to note, though, that any credible means of studying or modifying NPY-dependent feeding behavior must necessarily be highly selective, as NPY interacts with multiple receptor subtypes, as noted above (Dumont et al., 1992).

As used in this invention, the term "antagonist" refers to a compound which decreases the activity of a receptor. In the case of a G-protein coupled receptor, activation may be measured using any appropriate second messenger system which is coupled to the receptor in a cell or tissue in which the receptor is expressed. Some specific but by no means limiting examples of well-known second messenger systems are adenylate cyclase, intracellular calcium mobilization, ion channel activation, guanylate cyclase, and inositol phospholipid hydrolysis. Conversely, the term "agonist" refers to a compound which increases the activity of a receptor.

In order to test compounds for selective binding to the human Y5 receptor the cloned cDNAs encoding both the human and rat Y2 and Y4 (or PP) receptors have been used. The

human and rat Y5 receptors were disclosed in PCT International Application No. PCT/US95/15646, published June 6, 1996, and filed as a continuation in part of U.S. Serial No. 08/349,025, filed December 2, 1994, the contents of which are hereby incorporated by reference into this application. The human and rat Y2 receptors were disclosed in PCT International Application US95/01469, published August 10, 1995, as WO 95/21245, and filed as a continuation-in-part of U.S. 08/192,288, filed February 3, 1994, the contents of which are hereby incorporated by reference into this application. The human and rat Y4 receptors were disclosed in PCT International Application PCT/US94/14436, published July 6, 1995, as WO 95/17906, and filed as a continuation-in-part of U.S. 08/176,412, filed December 28, 1993, the contents of which are hereby incorporated by reference into this application. The Y1 receptor has been cloned from a variety of species including human, rat and mouse (Larhammar et al, 1992; Herzog et al, 1992; Eva et al, 1990; Eva et al, 1992).

The synthesis of novel aryl sulfonamide and sulfamide compounds are disclosed which bind selectively to the cloned human Y5 receptor compared to the other cloned human NPY receptors, and inhibit the activation of the cloned human Y5 receptor as measured in in vitro assays. The in vitro receptor binding and activation assays described hereinafter were performed using various cultured cell lines, each transfected with and expressing only a single Y-type receptor. In addition, the compounds of the present invention were shown to inhibit in animals either NPY-induced feeding behavior or feeding behavior exhibited by food-deprived animals.

This invention is also directed to the treatment of feeding disorders such as obesity and bulimia nervosa using the compounds described herein. In addition, the compounds of the present invention may also be used to

5 treat abnormal conditions such as sexual/reproductive disorders, depression, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure or sleep disturbances, or any condition in which antagonism of a Y5 receptor may be useful.

Summary of the Invention

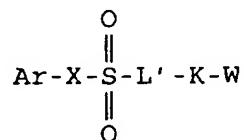
This invention is directed to novel aryl sulfonamide and sulfamide compounds which bind selectively to and inhibit the activity of the human Y5 receptor. This invention is also related to uses of these compounds for the treatment of feeding disorders such as obesity, anorexia nervosa, bulimia nervosa, and abnormal conditions such as sexual/reproductive disorders, depression, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure or sleep disturbances and for the treatment of any disease in which antagonism of a Y5 receptor may be useful.

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Detailed Description of the Invention

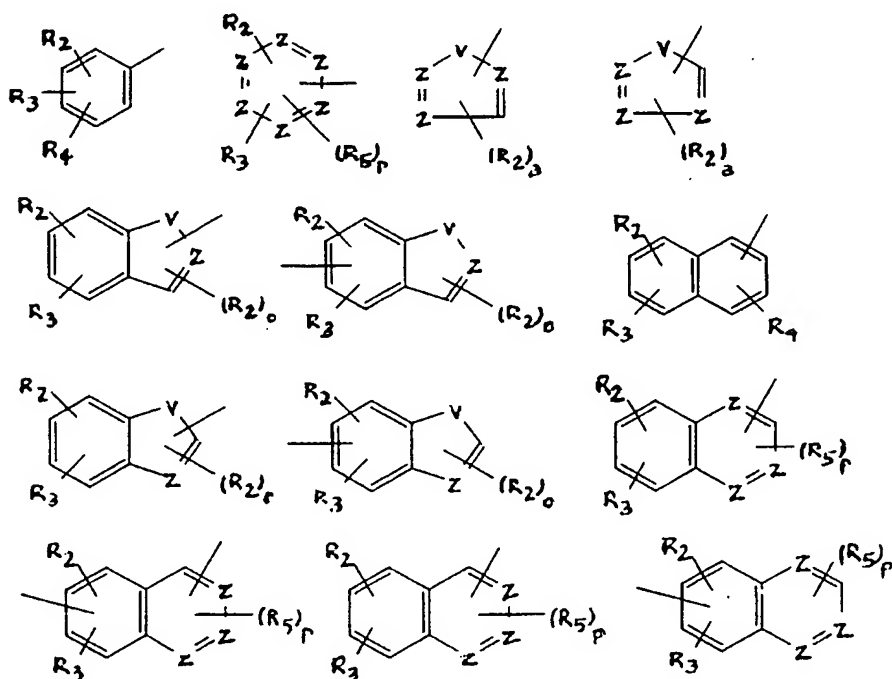
The present invention is directed to compounds having the structures:

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wherein Ar is



15

wherein each Z is independently N or C;

wherein each Y is independently N or C;

wherein p is an integer from 0 to 2;

wherein  $o$  is an integer from 0 to 1 and  $a$  is an integer from 0 to 3;

wherein  $V$  is S, O, N, or  $NR_5$ ;

5

wherein  $X$  is a single bond or  $-NH-$ ;

wherein each  $R_2$  is independently H; F; Cl; Br; I;  $NO_2$ ; OH;  $C_1-C_4$  alkyl;  $C_2-C_4$  alkenyl;  $C_1-C_4$  alkoxy;  $C_1-C_4$  hydroxyalkyl;  $C_1-C_4$  methoxyalkyl;  $C_1-C_4$  monohaloalkyl;  $C_1-C_4$  polyhaloalkyl;  $N(R_5)_2$ ;  $NHCO_2R_5$ ;  $N(COR_5)_2$ ;  $NHCONHR_5$ ;  $NHSO_2R_5$ ;  $N(SO_2R_5)_2$ ;  $CO_2R_5$ ;  $CON(R_5)_2$ ;  $SO_2N(R_5)_2$ ; phenoxy; phenyl; pyridyl; thiophenyl; naphthyl; phthalimide;  $C_5-C_7$  lactam,  $C_5-C_7$  cyclic imide,  $C_5-C_7$  cyclic amino; wherein the phthalimide, lactam, cyclic imide, or cyclic amine is linked by nitrogen; and wherein the phenoxy, phenyl, pyridyl, thiophenyl, naphthyl, phthalimide, lactam, cyclic imide, or cyclic amine is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkylthio, or  $NO_2$ ;

20

wherein each  $R_3$  is independently H; F; Cl; Br; I;  $NO_2$ ; OH;  $C_1-C_4$  alkyl;  $C_2-C_4$  alkenyl;  $C_1-C_4$  alkoxy;  $C_1-C_4$  hydroxyalkyl;  $C_1-C_4$  methoxyalkyl;  $C_1-C_4$  monohaloalkyl;  $C_1-C_4$  polyhaloalkyl;  $N(R_5)_2$ ;  $NHCO_2R_5$ ;  $N(COR_5)_2$ ;  $NHCONHR_5$ ;  $NHSO_2R_5$ ;  $N(SO_2R_5)_2$ ;  $CO_2R_5$ ;  $CON(R_5)_2$ ;  $SO_2N(R_5)_2$ ; or  $R_2$  and  $R_3$  present on adjacent carbon atoms can constitute  $C_5-C_7$  cycloalkyl,  $C_5-C_7$  heterocycloalkyl or  $C_5-C_7$  heteroaryl;

25

wherein each  $R_4$  is independently H; F; Cl; Br; I;  $NO_2$ ; OH;  $C_1-C_4$  alkyl;  $C_1-C_4$  alkoxy;  $C_1-C_4$  hydroxyalkyl;  $C_1-C_4$  methoxyalkyl;  $C_1-C_4$  monohaloalkyl;  $C_1-C_4$  polyhaloalkyl;  $N(R_5)_2$ ;  $NHCO_2R_5$ ;  $N(COR_5)_2$ ;  $NHCONHR_5$ ;  $NHSO_2R_5$ ;  $N(SO_2R_5)_2$ ;  $CO_2R_5$ ;  $CON(R_5)_2$ ; or  $SO_2N(R_5)_2$ ;

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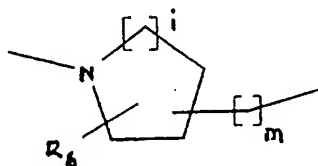


-9-

wherein each  $R_5$  is independently H;  $C_1-C_3$  alkyl;  $C_1-C_3$  monohaloalkyl; or  $C_1-C_3$  polyhaloalkyl;

wherein  $L'$  is  $-NR_1-L-$  or

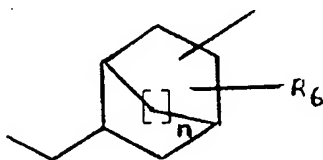
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wherein  $L$  is  $C_3-C_9$  alkyl;  $C_3-C_9$  alkenyl;  $C_3-C_9$  alkynyl;

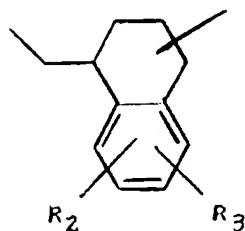
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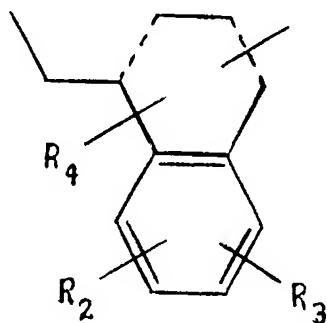


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or



- 5 wherein  $R_1$  is H; or  $C_1-C_3$  straight chained alkyl;
- wherein the alkyl, alkenyl or alkynyl is substituted with H,  $OR_5$ , CN,  $C_1-C_6$  alkyl,  $CH_2OR_5$ ,  $CON(R_5)_2$ ,  $CO_2R_5$ , phenyl, pyridyl, thiophenyl or naphthyl;
- 10 wherein one dashed line is a double bond and the other dashed line is a single bond;
- wherein each  $R_k$  is independently H; CN;  $OR_5$ ;  $C_1-C_5$  alkyl;  $CH_2OR_5$ ;  $CON(R_5)_2$ ;  $CO_2R_5$ ; phenyl; pyridyl; thiophenyl or naphthyl; wherein the phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkylthio, or  $NO_2$ ;
- 15
- wherein  $i$  is an integer from 1 to 4; wherein  $n$  is an integer from 0 to 3; wherein  $m$  is an integer from 0 to 3;
- 20
- wherein  $K$  is  $-CH_2-NR_{10}-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-(CH_2)_j-$ ;  $-CH_2-NH-CO-NH-(CH_2)_j-$ ;  $-CO-NH-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CS-(CH_2)_j-$ ;  $-CH_2-NH-CS-NH-(CH_2)_j-$ ;  $-CS-NH-$

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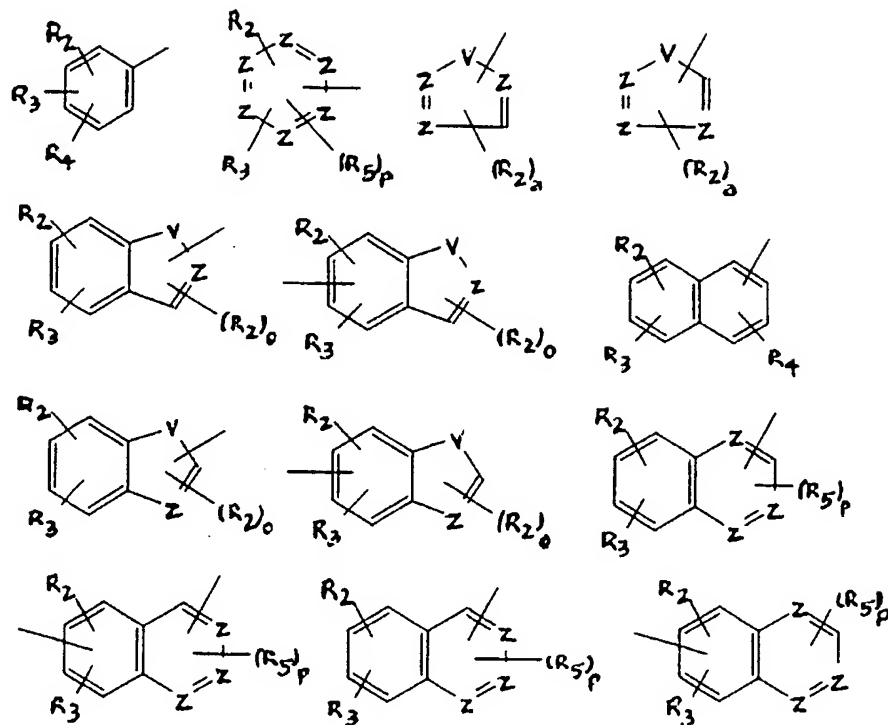
$\text{CHR}_7 - (\text{CH}_2)_j -$ ;  $-\text{CH}_2 - \text{NR}_{10} - \text{CS} - \text{CHR}_7 - (\text{CH}_2)_j$ ; or  $-\text{CH}_2 - \text{N} = \text{CSR}_1 - \text{NH} - (\text{CH}_2)_j$ ;

wherein  $j$  is an integer from 0 to 3;

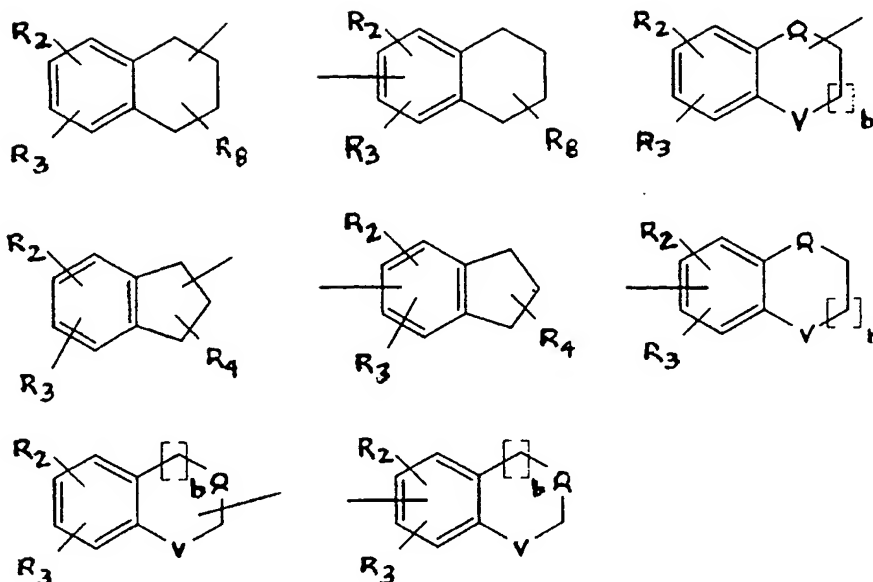
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wherein  $R_7$  is H;  $\text{C}_1 - \text{C}_6$  alkyl;  $\text{CH}_2\text{OR}_5$ ;  $-(\text{CH}_2)_f\text{NHCO}_2\text{R}_5$ ;  $(\text{CH}_2)_p\text{NHSO}_2\text{R}_5$ ;  $\text{CH}_2\text{N}(\text{R}_{11})_2$ ; phenyl; pyridyl; thiophenyl; or naphthyl;

wherein W is



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wherein Q is O; S; N; NR<sub>9</sub>; or C(R<sub>5</sub>)<sub>2</sub>;

5 wherein b is an integer from 1 to 2;

wherein R<sub>8</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; =O; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl;  
 10 N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; or SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;

wherein R<sub>9</sub> is H; C<sub>1</sub>-C<sub>3</sub> alkyl; COR<sub>5</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>;

15 wherein R<sub>10</sub> is H; or C<sub>1</sub>-C<sub>6</sub> alkyl;

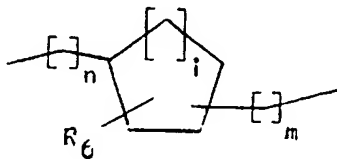
wherein R<sub>11</sub> is H; COR<sub>5</sub>; COR<sub>12</sub>; SO<sub>2</sub>R<sub>5</sub>; SO<sub>2</sub>R<sub>12</sub>; and

wherein  $R_{12}$  is phenoxy; phenyl, pyridyl; thiophenyl; or naphthyl; wherein the phenoxy, phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkylthio,  $NO_2$ , phenyl, pyridyl or thiophenyl; or a pharmaceutically acceptable salt thereof.

The invention also provides for the (+) and (-) enantiomers of the compounds described herein.

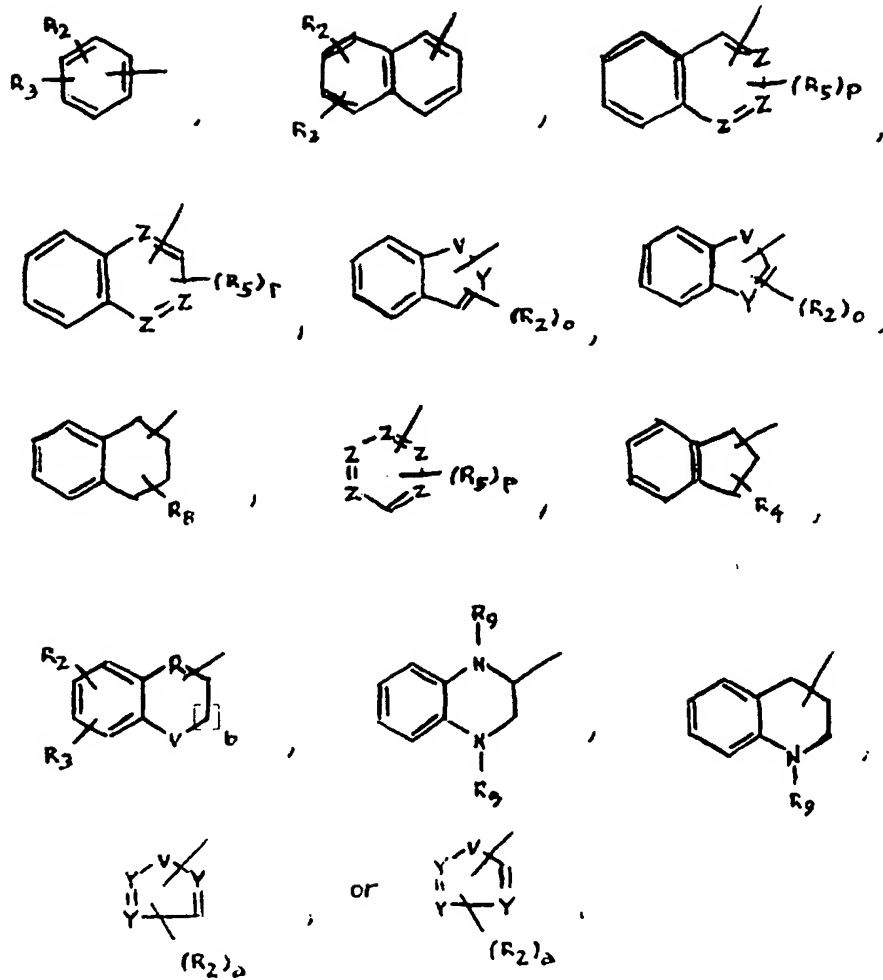
In one embodiment the invention provides for a compound as described above, where  $R_1$  is H;

where L is selected from  $C_3-C_9$  alkyl or



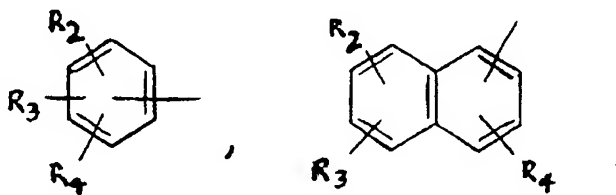
where the alkyl is substituted with H,  $OR_5$ , CN,  $C_1-C_6$  alkyl,  $CH_2OR_5$ ,  $CON(R_5)_2$ ,  $CO_2R_5$ , phenyl, pyridyl, thiophenyl or naphthyl; and

where W is

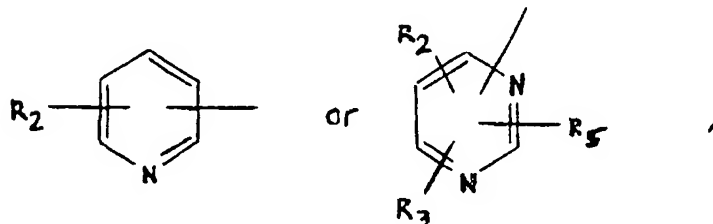


In other embodiments of the present invention, the compounds may have the structures where Ar is selected from:

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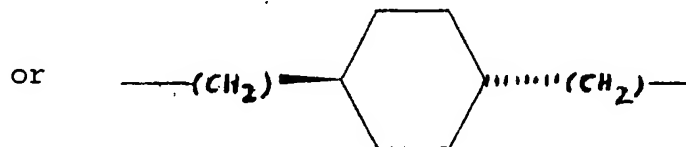
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where each of  $R_2$ ,  $R_3$  and  $R_4$  is independently H; F, Cl, Br or I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl; or  $\text{N}(\text{R}_5)_2$ ; where X is a single bond; where each  $R_5$  is independently  $\text{C}_1\text{-C}_3$  alkyl;

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where L is selected from  $\text{C}_5\text{-alkyl}$  or  $\text{C}_7\text{-alkyl}$ ;

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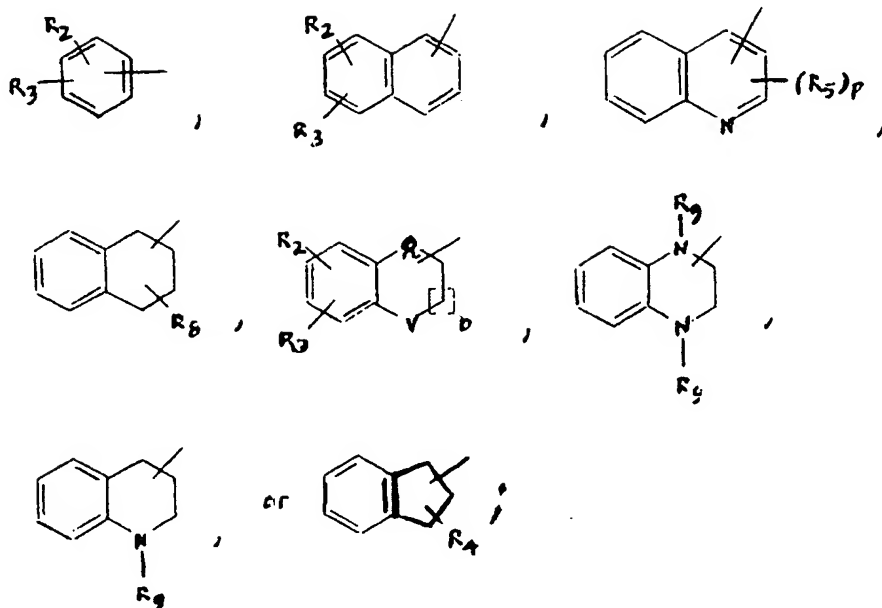


where  $R_7$  is H;  $\text{CH}_2\text{OH}$ ; or  $\text{CH}_2\text{OR}_5$ ;

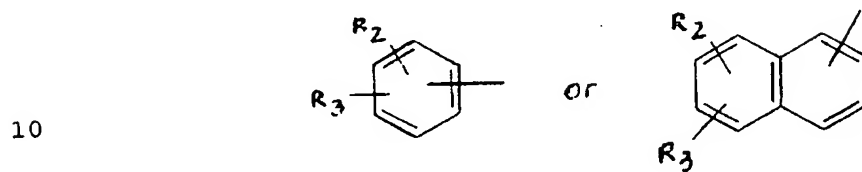


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where W is

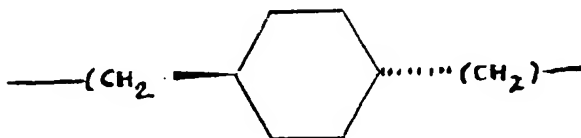
and where  $R_9$  is H; or  $C_1-C_3$  alkyl.

5 In other embodiments of the present invention Ar is selected from:



L is

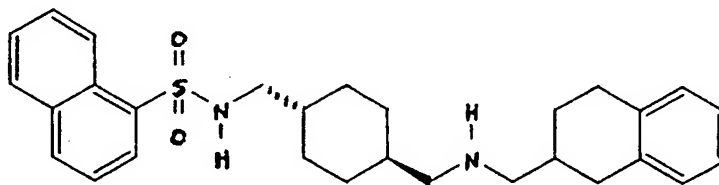
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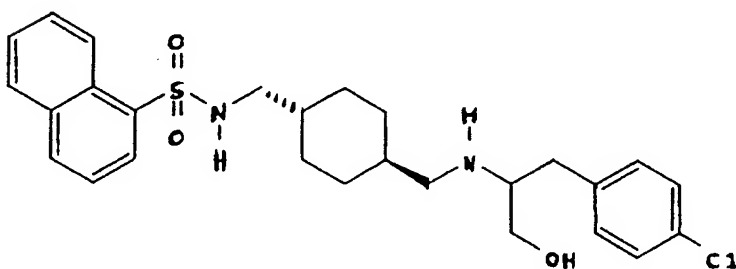
and K is  $-\text{CH}_2-\text{NR}_{10}-\text{CHR}_7-(\text{CH}_2)_3-$ .

Additional embodiments of the present invention include the compounds selected from the group consisting of:

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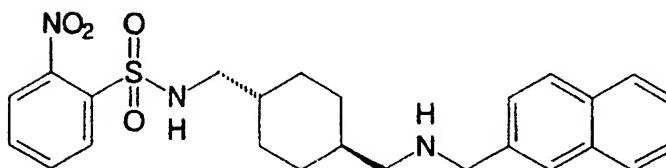


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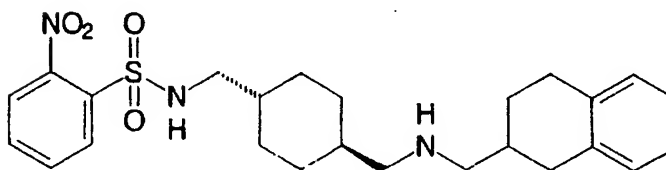
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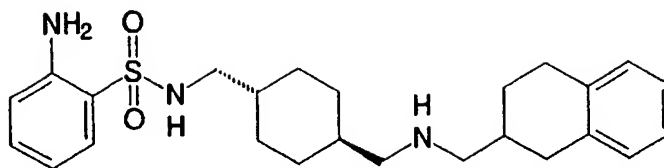
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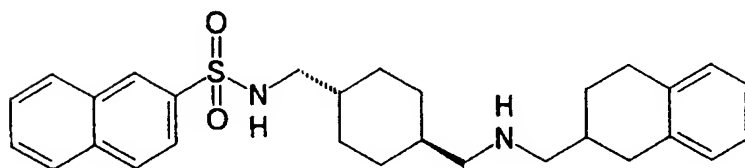


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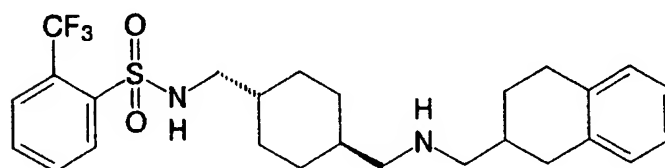


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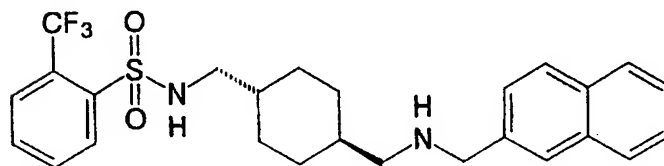


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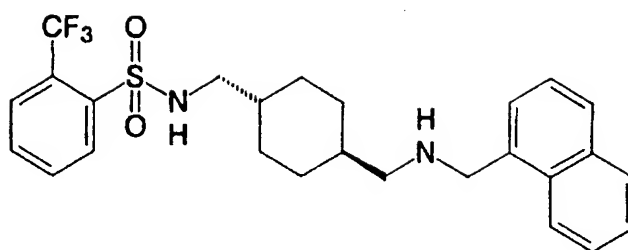
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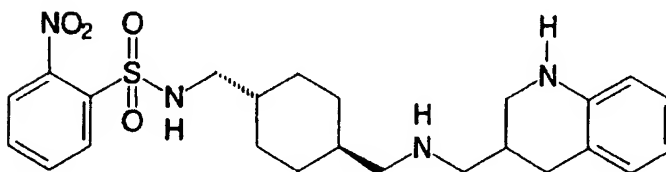
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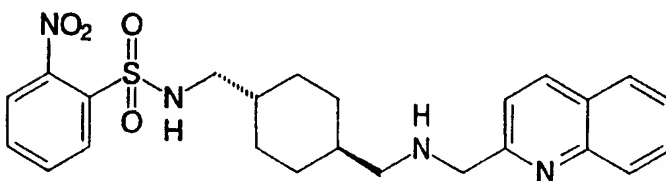
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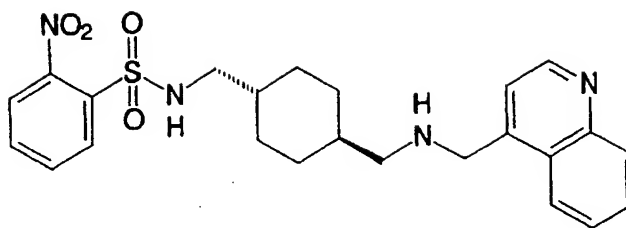
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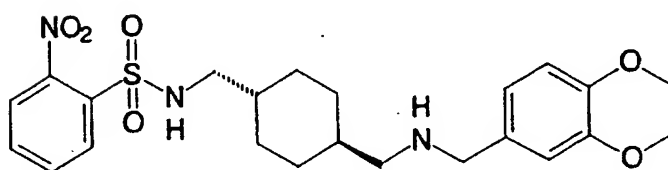
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or

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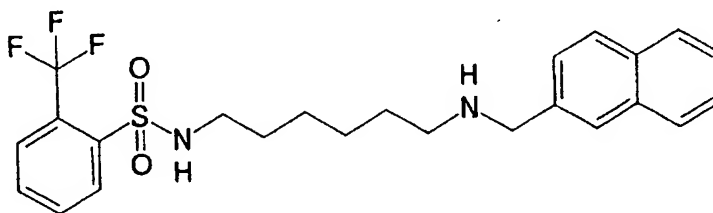
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Additional embodiments of the present invention include those in which L is C<sub>5</sub>-alkyl or C<sub>7</sub>-alkyl.

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In an embodiment of the invention the compounds have the structure:

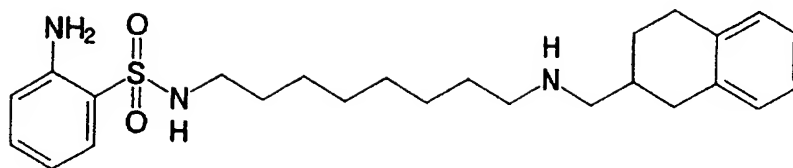
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or

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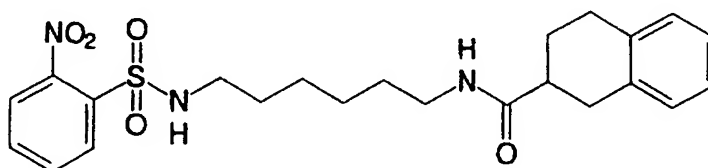


In one embodiment of the invention K is  
 $-\text{CH}_2-\text{NR}_{10}-\text{CO}-(\text{CH}_2)_j-$ .

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In another embodiment of the invention the compound has  
 the structure:

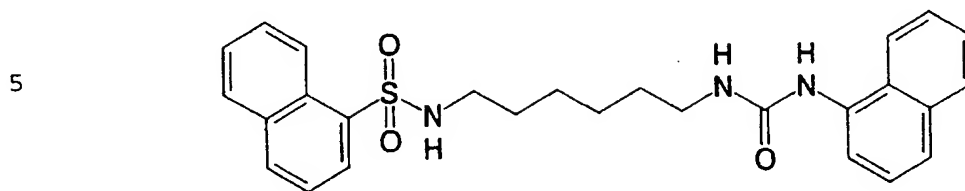
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In yet another embodiment of the present invention K is  
 $-\text{CH}_2-\text{NH}-\text{CO}-\text{NH}-(\text{CH}_2)_j-$ .

In a further embodiment of the invention the compound has the structure:



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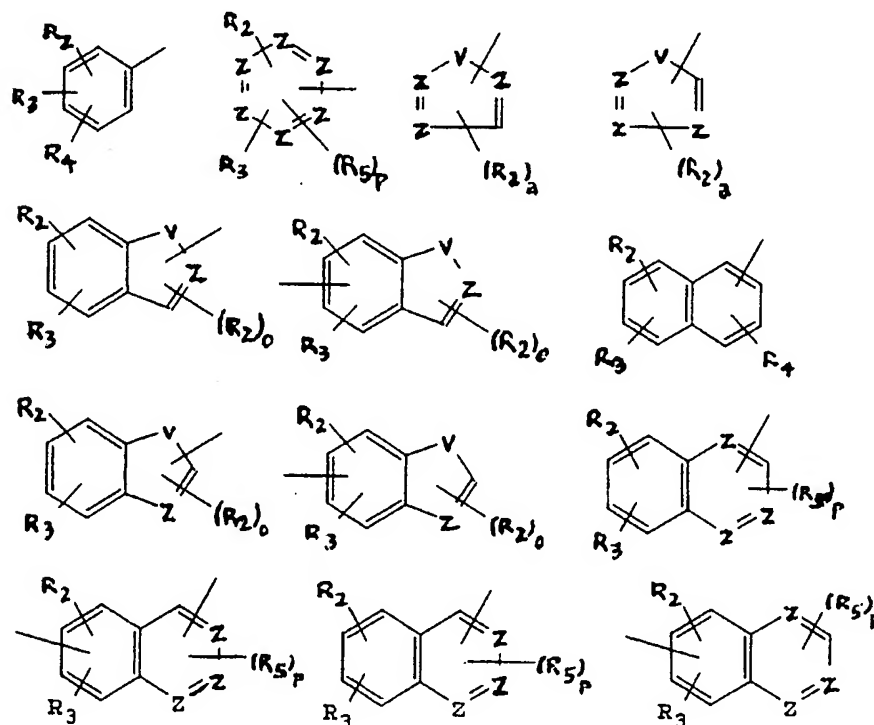
The invention also provides for a method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound effective to decrease the consumption of food by the subject so as to thereby modify feeding behavior of the

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subject, where the compound has the structure:



wherein Ar is



5 wherein each Z is independently N or C;

wherein each Y is independently N or C;

wherein p is an integer from 0 to 2;

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wherein o is an integer from 0 to 1 and a is an integer from 0 to 3;

wherein V is S, O, N, or  $NR_5$ ;

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wherein X is a single bond or  $-NH-$ ;



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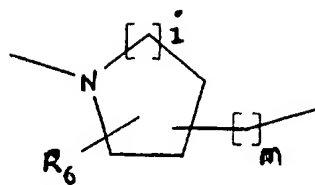
wherein each  $R_2$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_2\text{-C}_4$  alkenyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ;  $\text{SO}_2\text{N}(\text{R}_5)_2$ ; phenoxy; phenyl; pyridyl; thiophenyl; naphthyl; phthalimide;  $\text{C}_5\text{-C}_7$  lactam,  $\text{C}_5\text{-C}_7$  cyclic imide,  $\text{C}_5\text{-C}_7$  cyclic amino; wherein the phthalimide, lactam, cyclic imide, or cyclic amine is linked by nitrogen; and wherein the phenoxy, phenyl, pyridyl, thiophenyl, naphthyl, phthalimide, lactam, cyclic imide, or cyclic amine is substituted with H, F, Cl, Br, I,  $\text{CF}_3$ ,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  alkoxy,  $\text{C}_1\text{-C}_4$  alkylthio, or  $\text{NO}_2$ ;

wherein each  $R_3$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_2\text{-C}_4$  alkenyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ;  $\text{SO}_2\text{N}(\text{R}_5)_2$ ; or  $\text{R}_2$  and  $\text{R}_3$  present on adjacent carbon atoms can constitute  $\text{C}_5\text{-C}_7$  cycloalkyl,  $\text{C}_5\text{-C}_7$  heterocycloalkyl or  $\text{C}_5\text{-C}_7$  heteroaryl;

wherein each  $R_4$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ; or  $\text{SO}_2\text{N}(\text{R}_5)_2$ ;

wherein each  $R_5$  is independently H;  $\text{C}_1\text{-C}_3$  alkyl;  $\text{C}_1\text{-C}_3$  monohaloalkyl; or  $\text{C}_1\text{-C}_3$  polyhaloalkyl;

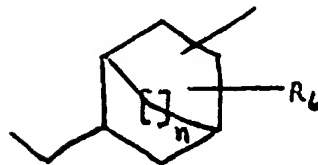
wherein  $\text{L}'$  is  $\text{-NR}_1\text{-L-}$  or



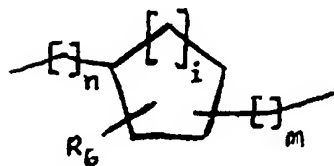
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wherein L is C<sub>3</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> alkenyl; C<sub>3</sub>-C<sub>6</sub> alkynyl;

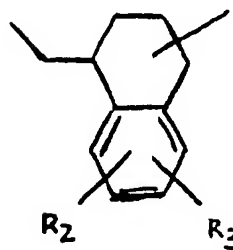
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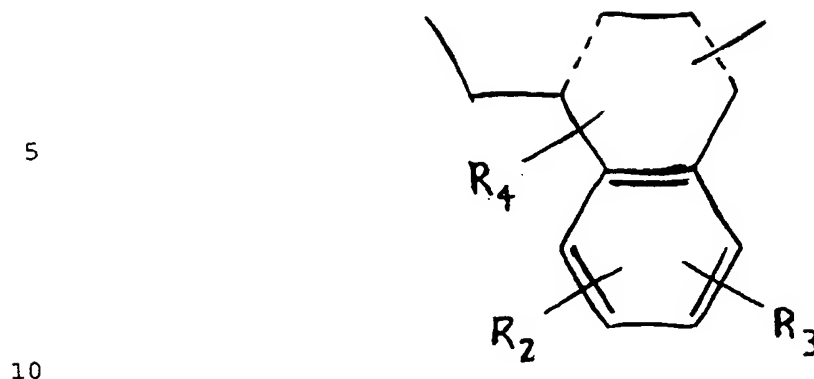
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or

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wherein  $R_1$  is H; or  $C_1$ - $C_3$  straight chained alkyl;

15 wherein the alkyl, alkenyl or alkynyl is substituted with H,  $OR_5$ , CN,  $C_1$ - $C_6$  alkyl,  $CH_2OR_5$ ,  $CON(R_5)_2$ ,  $CO_2R_5$ , phenyl, pyridyl, thiophenyl or naphthyl;

wherein one dashed line is a double bond and the other dashed line is a single bond;

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wherein each  $R_6$  is independently H; CN;  $OR_5$ ;  $C_1$ - $C_5$  alkyl;  $CH_2OR_5$ ;  $CON(R_5)_2$ ;  $CO_2R_5$ ; phenyl; pyridyl; thiophenyl or naphthyl; wherein the phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio, or  $NO_2$ ;

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wherein  $i$  is an integer from 1 to 4; wherein  $n$  is an integer from 0 to 3; wherein  $m$  is an integer from 0 to 3;

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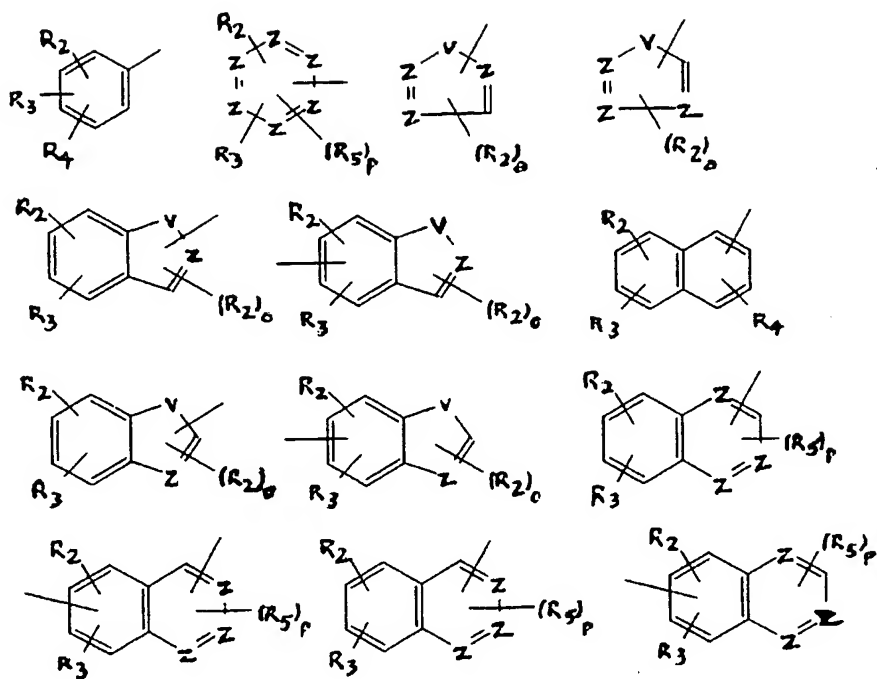
wherein  $K$  is  $-CH_2-NR_{1c}-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-(CH_2)_j-$ ;  $-CH_2-NH-CO-NH-(CH_2)_j-$ ;  $-CO-NH-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{1c}-CO-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{13}-CS-(CH_2)_j-$ ;  $-CH_2-NH-CS-NH-(CH_2)_j-$ ;  $-CS-NH-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{13}-CS-CHR_7-(CH_2)_j$ ; or  $-CH_2-N=CSR_1-NH-(CH_2)_j$ ;

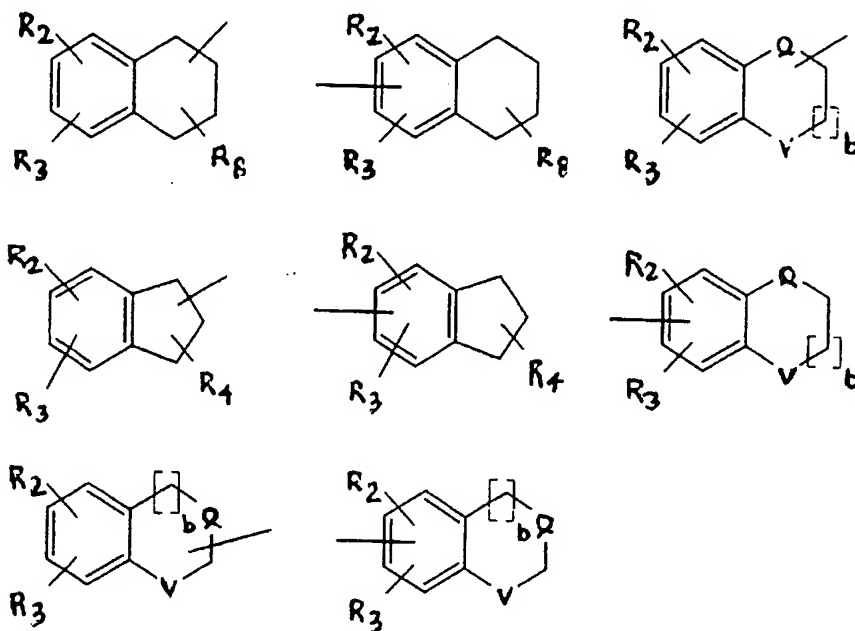
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wherein  $j$  is an integer from 0 to 3;

wherein  $R_7$  is H;  $C_1$ - $C_6$  alkyl;  $CH_2OR_5$ ;  $(CH_2)_pNHCO_2R_5$ ;  
5  $(CH_2)_pNHSO_2R_5$ ;  $CH_2N(R_{11})_2$ ; phenyl; pyridyl; thiophenyl; or  
naphthyl;

wherein W is





wherein Q is O; S; N; NR<sub>9</sub>; or C(R<sub>5</sub>)<sub>2</sub>;

5 wherein b is an integer from 1 to 2;

wherein R<sub>8</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; =O; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl;  
 10 N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; or SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;

wherein R<sub>9</sub> is H; C<sub>1</sub>-C<sub>3</sub> alkyl; COR<sub>5</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>;

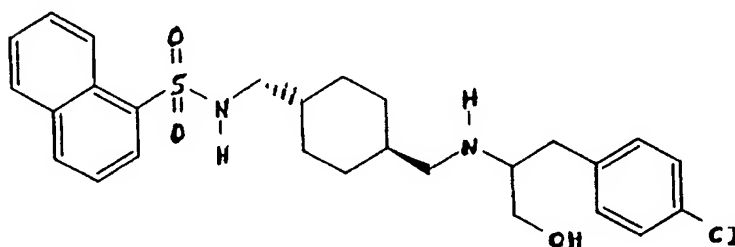
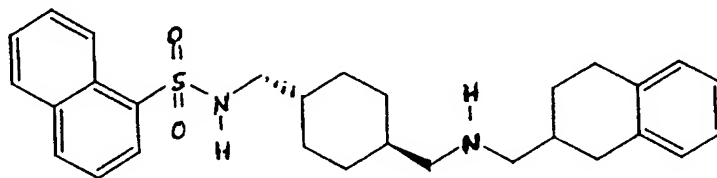
15 wherein R<sub>10</sub> is H; or C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein R<sub>11</sub> is H; COR<sub>5</sub>; COR<sub>12</sub>; SO<sub>2</sub>R<sub>5</sub>; SO<sub>2</sub>R<sub>12</sub>; and

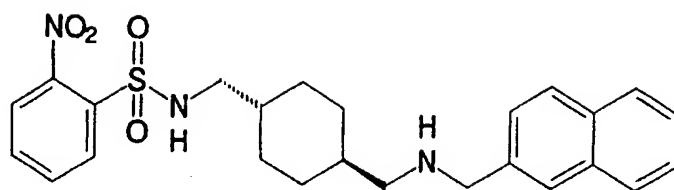
wherein  $R_{12}$  is phenoxy; phenyl, pyridyl; thiophenyl; or naphthyl; wherein the phenoxy, phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkylthio,  $NO_2$ , phenyl, pyridyl or thiophenyl; or a pharmaceutically acceptable salt thereof.

In one embodiment of the method described above the subject is a vertebrate, a mammal, a human or a canine. In another embodiment the compound is administered in combination with food.

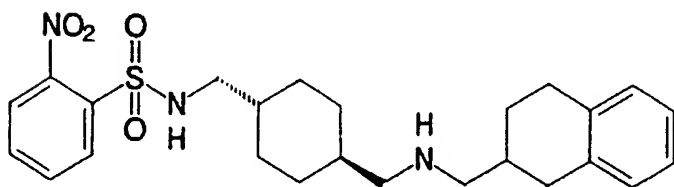
The invention also provides for a method of modifying feeding behavior where the compound has the structure:



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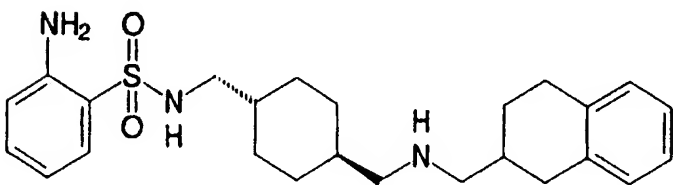


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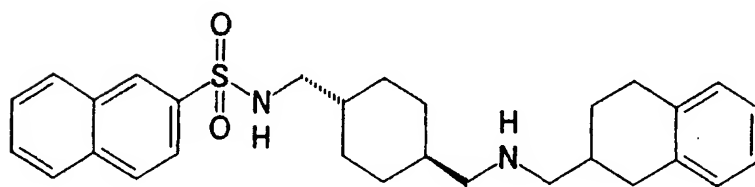


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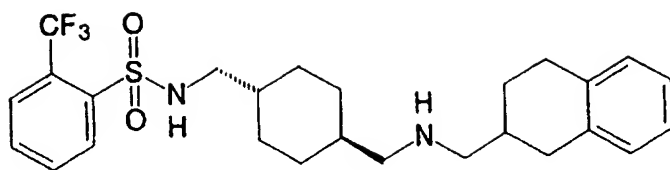


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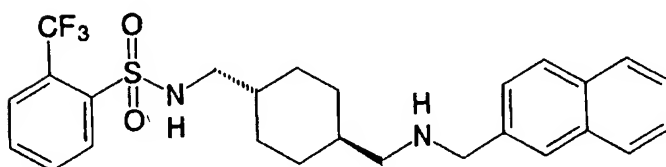
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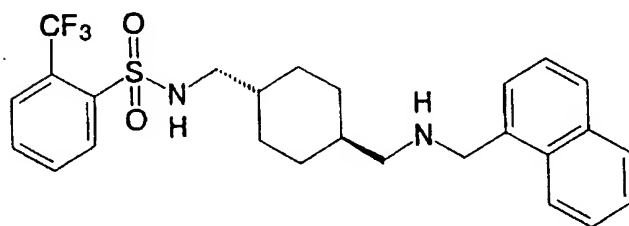


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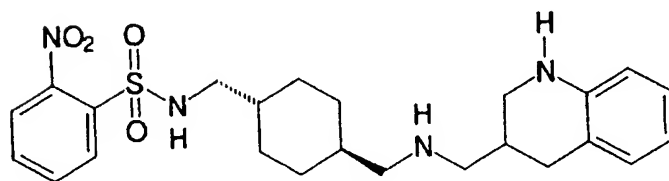
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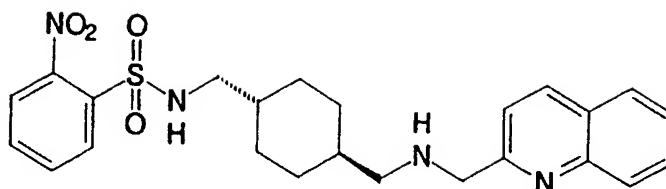
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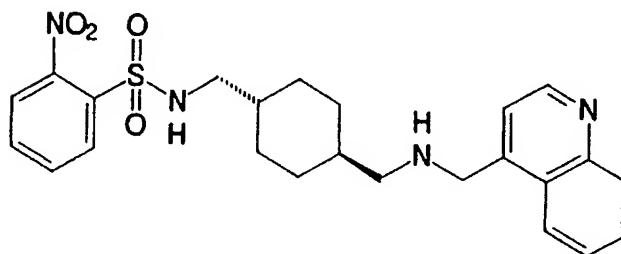
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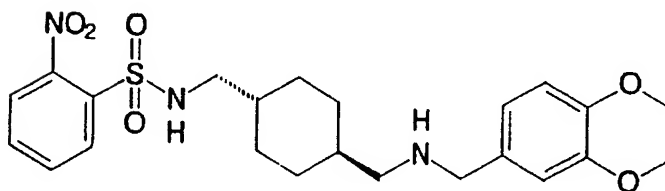


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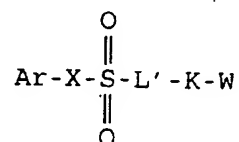
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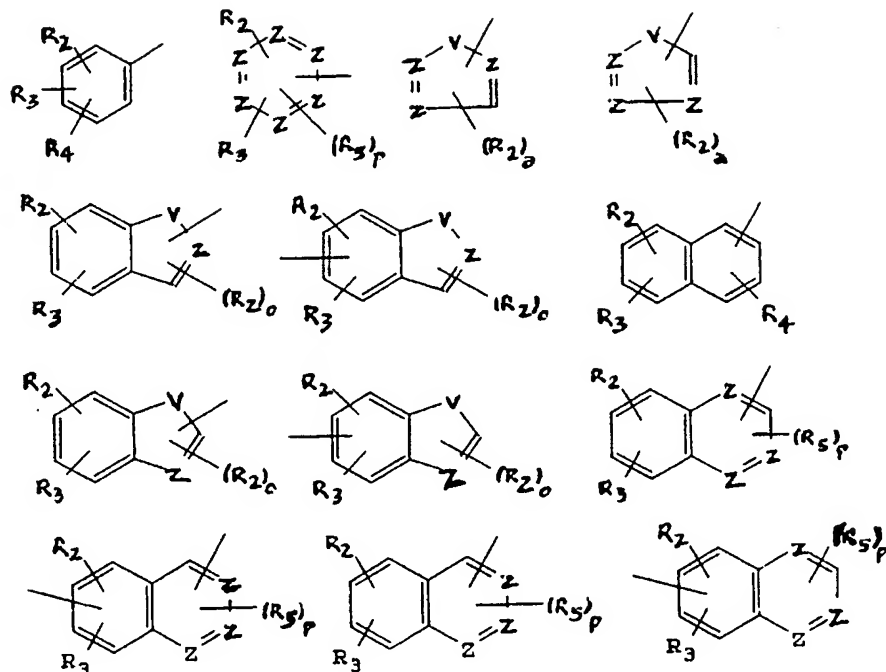
The invention further provides a method of treating a feeding disorder in a subject which comprises administering to the subject an amount of a compound effective to decrease consumption of food by the subject, where the compound has the structure:

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wherein Ar is



5 wherein each Z is independently N or C;

wherein each Y is independently N or C;

wherein p is an integer from 0 to 2;

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wherein o is an integer from 0 to 1 and a is an integer from 0 to 3;

wherein V is S, O, N, or NR<sub>5</sub>;

15

wherein X is a single bond or -NH-;

wherein each  $R_2$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_2\text{-C}_4$  alkenyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ;  $\text{SO}_2\text{N}(\text{R}_5)_2$ ; phenoxy; phenyl; pyridyl; thiophenyl; naphthyl; phthalimide;  $\text{C}_5\text{-C}_7$  lactam,  $\text{C}_5\text{-C}_7$  cyclic imide,  $\text{C}_5\text{-C}_7$  cyclic amino; wherein the phthalimide, lactam, cyclic imide, or cyclic amine is linked by nitrogen; and wherein the phenoxy, phenyl, pyridyl, thiophenyl, naphthyl, phthalimide, lactam, cyclic imide, or cyclic amine is substituted with H, F, Cl, Br, I,  $\text{CF}_3$ ,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  alkoxy,  $\text{C}_1\text{-C}_4$  alkylthio, or  $\text{NO}_2$ ;

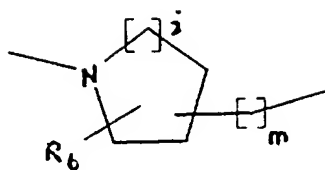
wherein each  $R_3$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_2\text{-C}_4$  alkenyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ;  $\text{SO}_2\text{N}(\text{R}_5)_2$ ; or  $\text{R}_2$  and  $\text{R}_3$  present on adjacent carbon atoms can constitute  $\text{C}_5\text{-C}_7$  cycloalkyl,  $\text{C}_5\text{-C}_7$  heterocycloalkyl or  $\text{C}_5\text{-C}_7$  heteroaryl;

wherein each  $R_4$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ; or  $\text{SO}_2\text{N}(\text{R}_5)_2$ ;

wherein each  $R_5$  is independently H;  $\text{C}_1\text{-C}_3$  alkyl;  $\text{C}_1\text{-C}_3$  monohaloalkyl; or  $\text{C}_1\text{-C}_3$  polyhaloalkyl;

wherein  $\text{L}'$  is  $\text{-NR}_1\text{-L-}$  or

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wherein L is  $C_3$ - $C_9$  alkyl;  $C_3$ - $C_9$  alkenyl;  $C_3$ - $C_9$  alkynyl;

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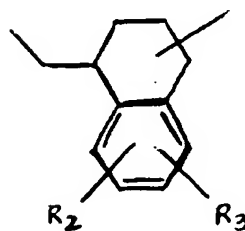


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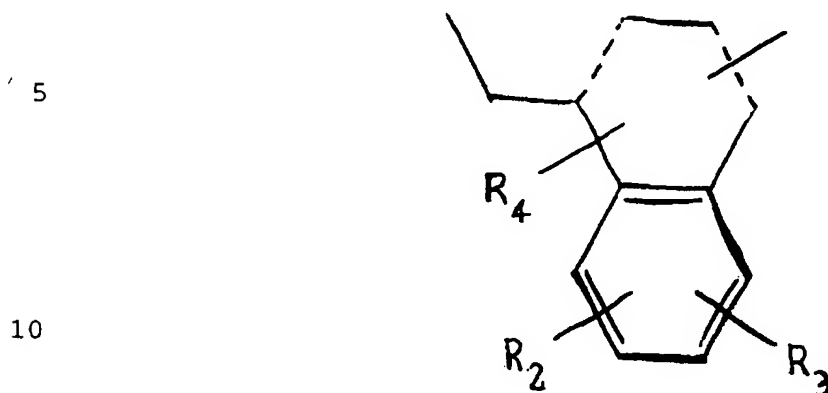


20

25



or



15 wherein  $R_1$  is H; or  $C_1$ - $C_3$  straight chained alkyl;

wherein the alkyl, alkenyl or alkynyl is substituted with H,  $OR_5$ , CN,  $C_1$ - $C_6$  alkyl,  $CH_2OR_5$ ,  $CON(R_5)_2$ ,  $CO_2R_5$ , phenyl, pyridyl, thiophenyl or naphthyl;

20 wherein one dashed line is a double bond and the other dashed line is a single bond;

25 wherein each  $R_6$  is independently H; CN;  $OR_5$ ;  $C_1$ - $C_5$  alkyl;  $CH_2OR_5$ ;  $CON(R_5)_2$ ;  $CO_2R_5$ ; phenyl; pyridyl; thiophenyl or naphthyl; wherein the phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio, or  $NO_2$ ;

30 wherein  $i$  is an integer from 1 to 4; wherein  $n$  is an integer from 0 to 3; wherein  $m$  is an integer from 0 to 3;

wherein  $K$  is  $-CH_2-NR_{10}-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-(CH_2)_j-$ ;  $-CH_2-NH-CO-NH-(CH_2)_j-$ ;  $-CO-NH-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CS-(CH_2)_j-$ ;  $-CH_2-NH-CS-NH-(CH_2)_i-$ ;  $-CS-NH-$

-39-

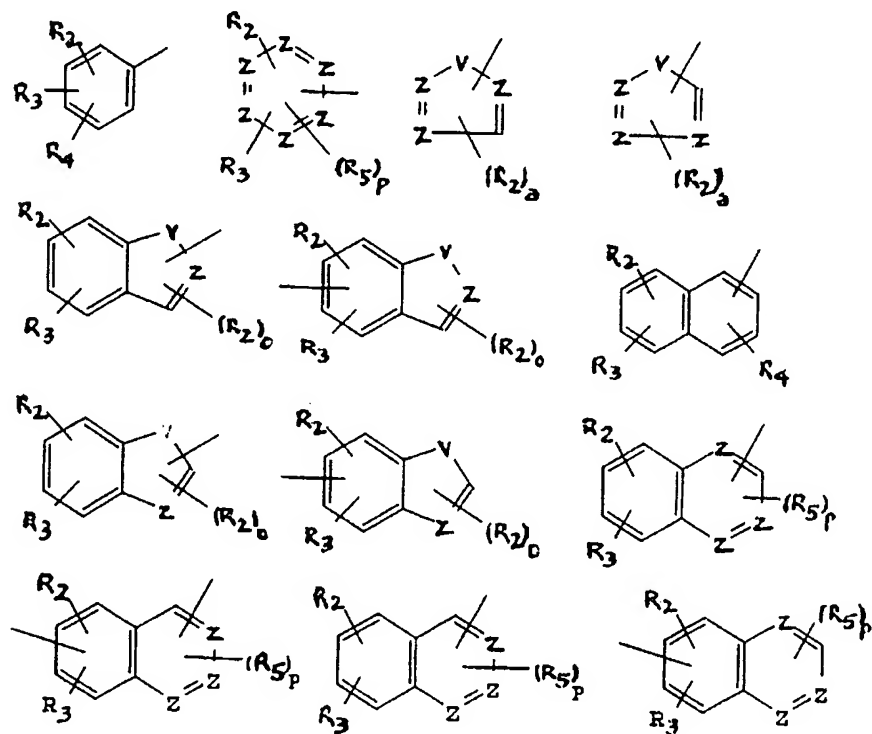
$\text{CHR}_7 - (\text{CH}_2)_j -$ ; or  $-\text{CH}_2 - \text{NR}_{10} - \text{CS} - \text{CHR}_7 - (\text{CH}_2)_j$ ; or  $-\text{CH}_2 - \text{N} = \text{CSR}_1 - \text{NH} - (\text{CH}_2)_j$ ;

wherein  $j$  is an integer from 0 to 3;

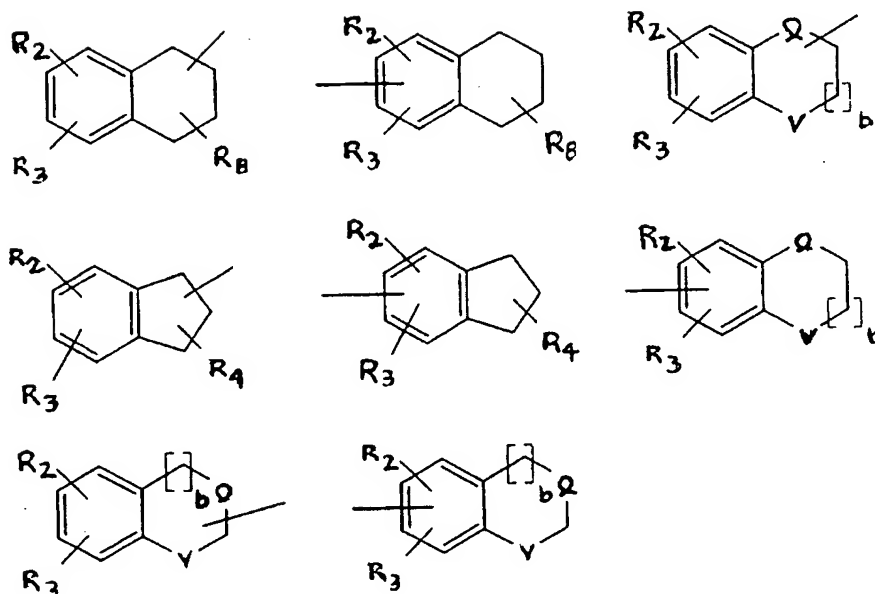
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wherein  $R_7$  is H;  $\text{C}_1 - \text{C}_6$  alkyl;  $\text{CH}_2\text{OR}_5$ ;  $(\text{CH}_2)_p\text{NHCO}_2\text{R}_5$ ;  $(\text{CH}_2)_p\text{NHSO}_2\text{R}_5$ ;  $\text{CH}_2\text{N}(\text{R}_{11})_2$ ; phenyl; pyridyl; thiophenyl; or naphthyl;

wherein W is







wherein Q is O; S; N; NR<sub>9</sub>; or C(R<sub>5</sub>)<sub>2</sub>;

5 wherein b is an integer from 1 to 2;

wherein R<sub>8</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; =O;  
 C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub>  
 methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl;  
 10 N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>;  
 N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; or SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;

wherein R<sub>9</sub> is H; C<sub>1</sub>-C<sub>3</sub> alkyl; COR<sub>5</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>;

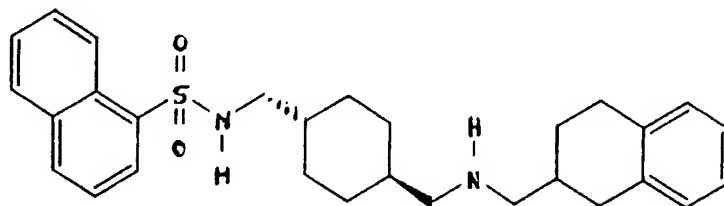
15 wherein R<sub>10</sub> is H; or C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein R<sub>11</sub> is H; COR<sub>5</sub>; COR<sub>12</sub>; SO<sub>2</sub>R<sub>5</sub>; SO<sub>2</sub>R<sub>12</sub>; and

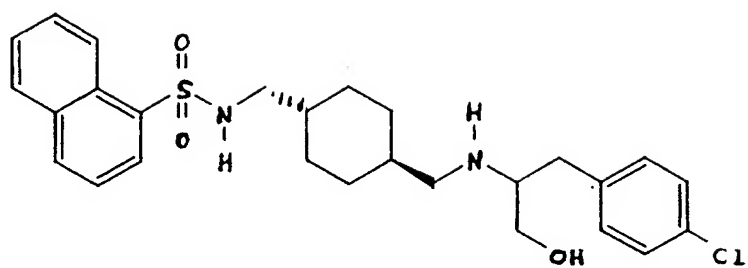
wherein  $R_{12}$  is phenoxy; phenyl, pyridyl; thiophenyl; or naphthyl; wherein the phenoxy, phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkylthio,  $NO_2$ , phenyl, pyridyl or thiophenyl; or a pharmaceutically acceptable salt thereof.

In an embodiment of the present invention the feeding disorder may be obesity or bulimia. In another embodiment of the present invention the subject is a vertebrate, a mammal, a human or a canine. The invention also provides for the decrease in the consumption of food by the subject by the compound inhibiting the activity of the subject's  $Y_5$  receptor.

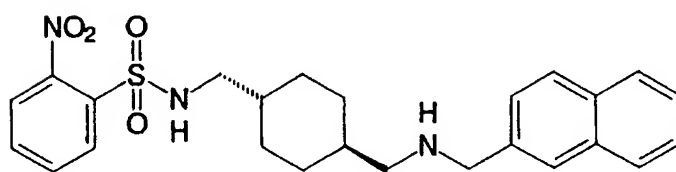
The invention further provides a method of treating a feeding disorder in a subject which comprises administering to the subject an amount of one of the following compounds:



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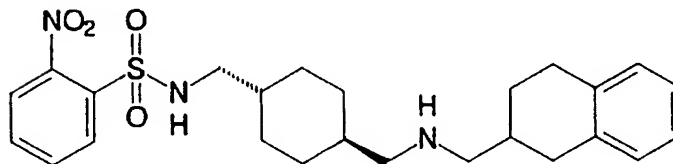


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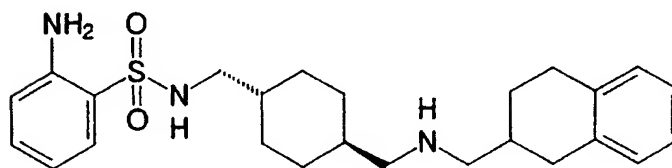
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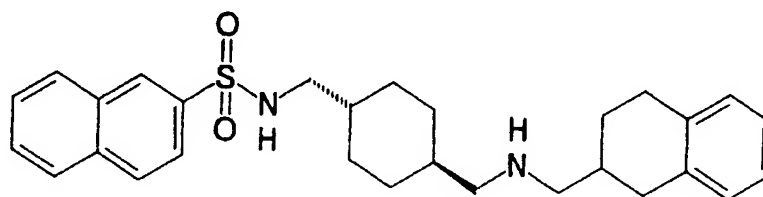
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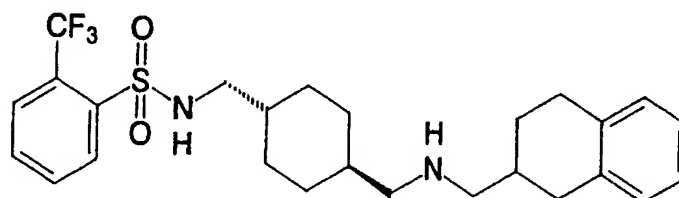


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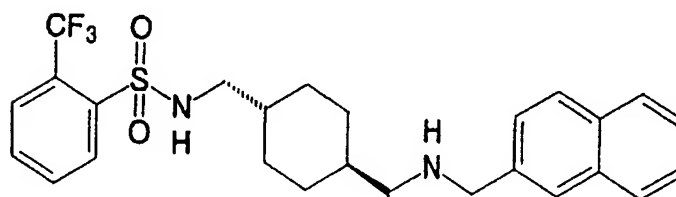
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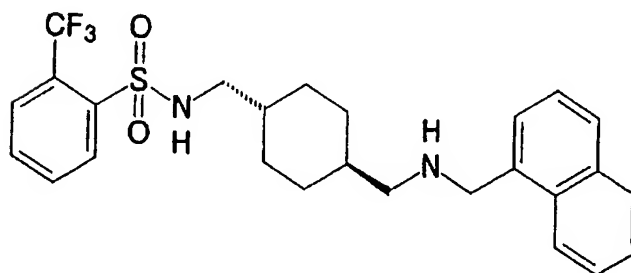


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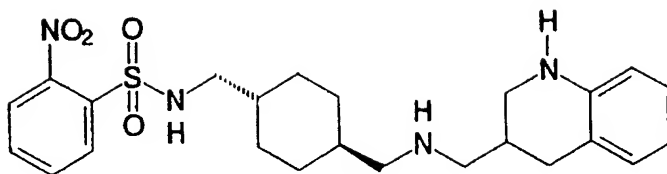
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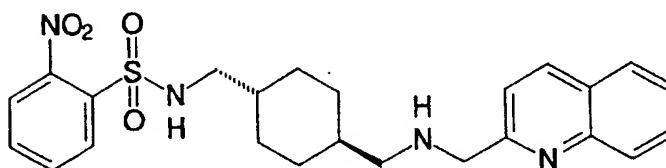
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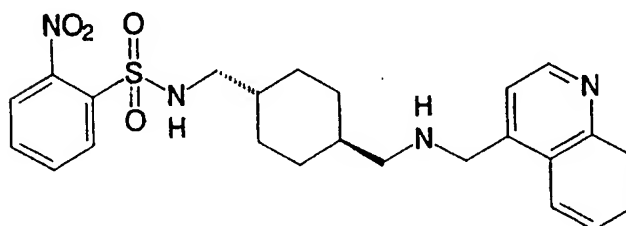
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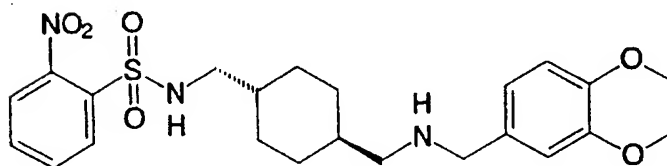


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25 or



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This invention also provides a method for treating a disorder in a subject which is alleviated by administering to the subject an amount of a compound described herein which is a Y5 receptor antagonist.

35

This invention additionally provides a method of treating obesity in a subject which comprises administering to the subject an amount of a Y5 receptor antagonist compound described herein.

5

This invention additionally provides a method of treating non-feeding disorders in a subject which comprises administering to the subject an amount of a compound described herein which is a Y5 receptor antagonist.

10

This invention further provides that any of the methods for treating may comprise administering to the subject a plurality of compounds described herein.

15 The invention also provides for the (-) and (+) enantiomers of the compounds of the subject application described herein. Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The salts include but are  
20 not limited to the acids and bases listed herein. The following inorganic acids; hydrochloric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. The organic acids; acetic acid, trifluoroacetic acid, formic acid, oxalic acid, malonic  
25 acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The following inorganic bases; ammonia, hydroxyethylamine and hydrazine.  
30 The following organic bases; methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of  
35 the compounds described herein.

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This invention further provides for the metabolites and precursors of the compounds of the present invention. The in vivo actions of numerous enzymes responsible for the generation of metabolites of pharmaceutical compounds are well-known in the art. For example, ethers may be modified to alcohols, or esters may be modified by esterases to yield acids as products. Knowledge of the activities of endogenous enzymes also allows the design of precursors or prodrugs of the compounds of the present invention, which when administered to a subject, such as a vertebrate or a human, are expected to yield metabolites which include the compounds of the present invention. For example, secondary amines may be modified by various substituents, such as methyl, alkanoyl, aroyl, or alkyl or aryl carbamates may be formed, which are expected to yield the compounds of the present invention when acted upon in vivo by endogenous enzymes. Such modifications are intended only as illustrative examples, and are not intended to limit the scope of the present invention, as such modifications and techniques therefor are well-known in the art.

The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the compounds described above and a pharmaceutically acceptable carrier. In the subject invention a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease. In one embodiment the therapeutically effective amount is an amount from about 0.01 mg per subject per day to about 500 mg per subject per day, preferably from about 0.1 mg per subject per day to about 60 mg per subject per day and most preferably from about 1 mg per subject per day to

about 20 mg per subject per day. In the practice of this invention the "pharmaceutically acceptable carrier" is any physiological carrier known to those of ordinary skill in the art useful in formulating pharmaceutical compositions.

5

In another embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In yet another embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch.

10  
15

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

20  
25  
30

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized

35



compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. Sterile liquid carriers can also be utilized for intranasal administration, for example with the use of a pressurized composition, or for inhalatory administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and

inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.

5 The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

10 The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

20 Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

25 One skilled in the art will readily appreciate that appropriate biological assays will be used to determine the therapeutic potential of the claimed compounds for treating the above noted disorders.

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This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

## Experimental Details

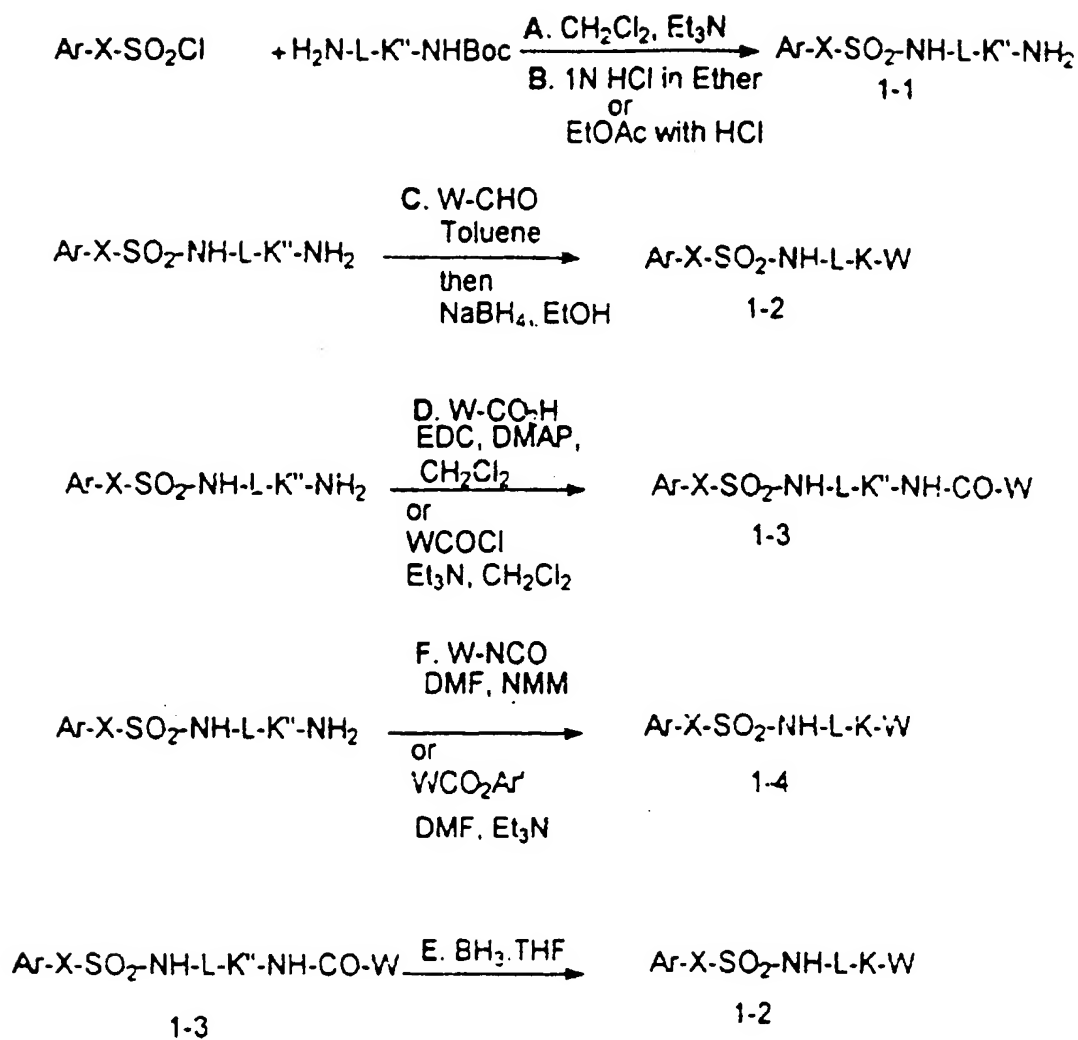
### **Synthetic Methods**

The compounds of the present invention may be synthesized according to the methods described in Schemes 1-4, as described herein. It is generally preferred that the respective product of each process step, as described hereinbelow, is separated and/or isolated prior to its use as starting material for subsequent steps. Separation and isolation can be effect by any suitable purifiaction prcedure such as, for example, evaporation, crystallization, column chromatography, thin layer chromatography, distillation, etc. While preferred reactants have been identified herein, it is further contemplated that the present invention would include chemical equivalents to each reactant specifically enumerated in this disclosure.

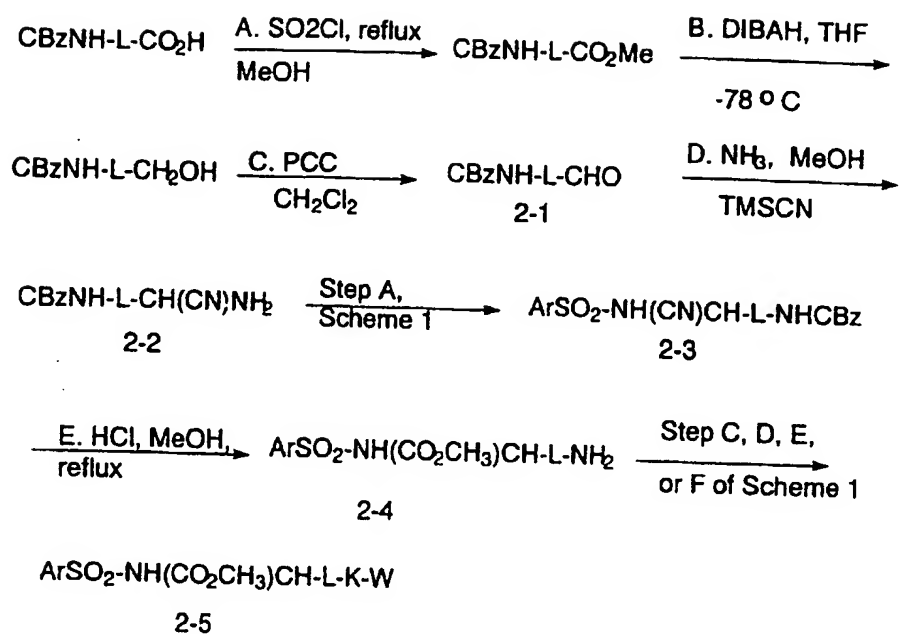
Temperatures are given in degrees Centigrade (°C). The structure of final products, intermediates and starting materials is confirmed by standard anlytical methods, e.g., microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR). Unless otherwise specified, chromatography is carried out using siilica gel. Flash chromatography refers to medium pressure column chromatography according to Still et al., J. Org. Chem. 43, 2921 (1978).

- 53 -

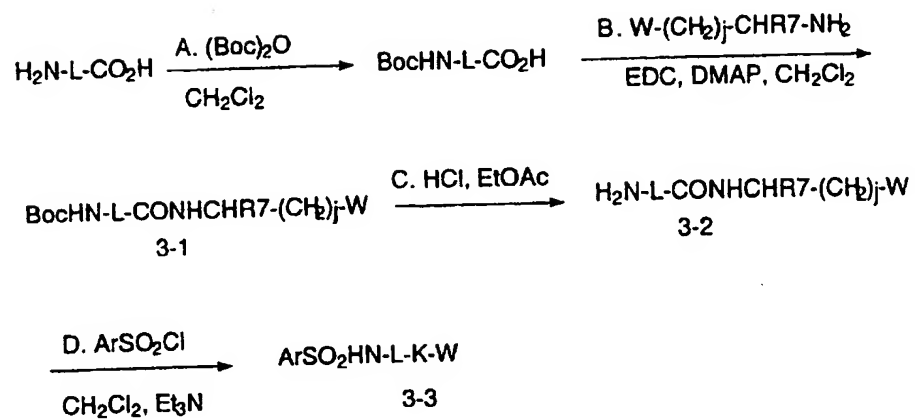
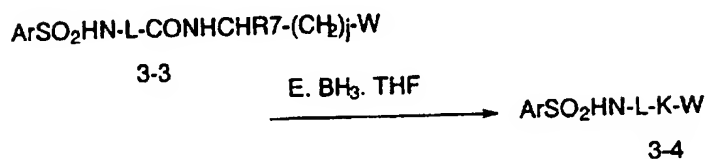
## Scheme 1



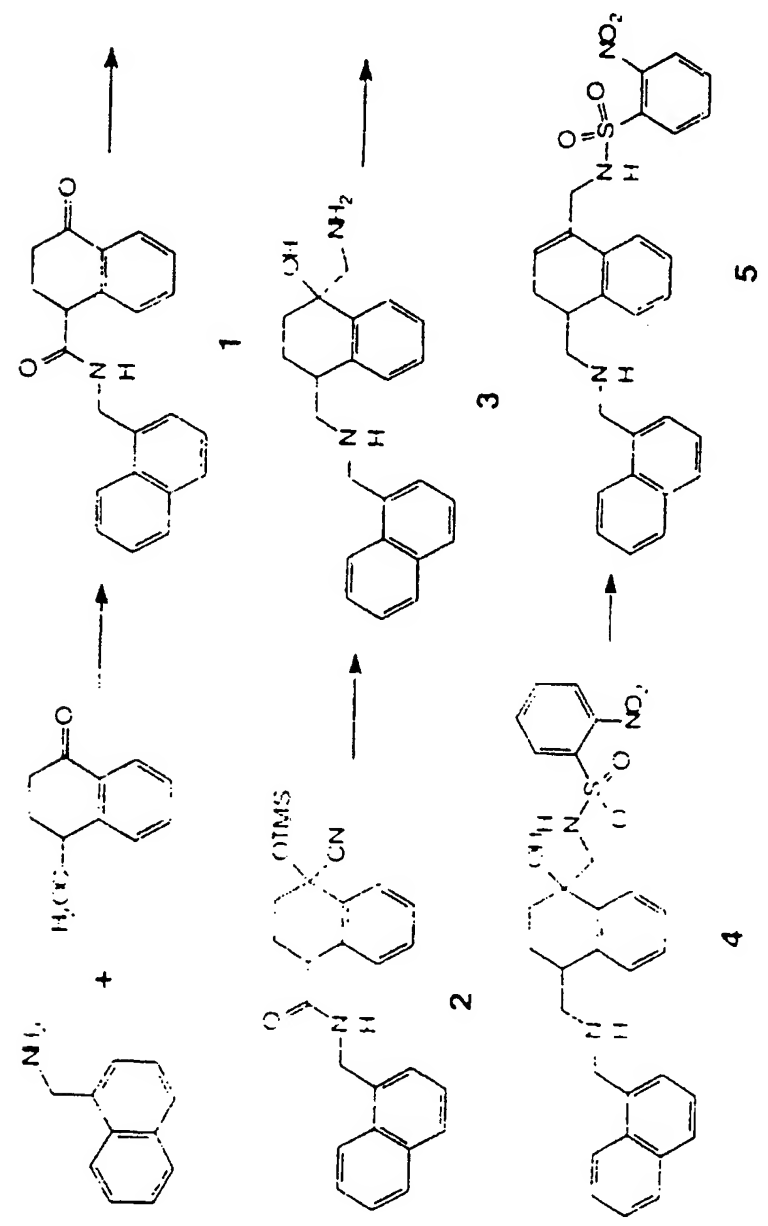
Scheme 2



## Scheme 3

Where K = -CONHCHR<sub>7</sub>(CH<sub>2</sub>)<sub>j</sub>-Where K = -CH<sub>2</sub>NHCHR<sub>7</sub>(CH<sub>2</sub>)<sub>j</sub>-

Scheme 4





### Synthesis of Compounds According to Scheme 1

Preparation of the compounds of the present invention having the structure shown in Formula 1-2, Scheme 1, was carried out using well-known methodology for the preparation of a sulfonamide or sulfamide from an amine. Preferably the appropriate arylsulfonyl or arylsulfamoyl halide, preferably the chloride (i.e., Ar-X-SO<sub>2</sub>Cl), is reacted with a monoprotected linear or cyclic alkylamine (Krapcho and Kuell, Synth. Comm. 20(16):2559-2564, 1990) comprising H<sub>2</sub>N-L-K'', where K'' comprises methylene, in the presence of a base such as a tertiary amine, e.g., triethylamine, dimethylaminopyridine, pyridine or the like, in an appropriate solvent (e.g. CHCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>) as shown in Scheme 1, step A, followed by deprotection of the resulting amine as shown in Scheme 1, Step B, all under mild conditions (typically room temperature), to yield the deprotected amine of Formula 1-1. Alternatively, the primary amine H<sub>2</sub>N-L may be replaced with a secondary amine wherein L comprises a piperidine. The arylsulfonyl or arylsulfamoyl halides are either known in the art or can be prepared according to methods well known in the art.

The deprotected amine may be converted to the product amine of Formula 1-2 by either a single step or two step reductive amination with an aryl substituted aldehyde W-CHO as shown in Scheme 1, Step C, in the presence of a solvent such as toluene or dioxane, at elevated temperature, followed by reduction using sodium borohydride in a solvent such as ethanol. The K'' amine and the aldehyde carbon attached to W together form K in the product.

Compounds of Formula 1-3 in Scheme 1, wherein R<sub>1</sub> is H and j=0 and K comprises an amide, may be synthesized from the compound of Formula 1-1 by amidation using suitable

methods such as those taught in "The Peptides," Vol. 1 (Gross and Meinehofer, Eds. Acaemic Press, N.Y., 1979). For example, the compound of Formula 1-1 may be treated with a carboxylic acid derivative of W in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and dimethylaminopyridine (DMAP) in a suitable solvent such as  $\text{CH}_2\text{Cl}_2$  as shown in Scheme 1, Step D, at room temperature in an inert atmosphere of argon or nitrogen, to yield the amide compound of Formula 1-3. As in the previous method, the K' amine and the carboxylic acid carbon attached to W together form K in the product.

Alternatively, the compound of Formula 1-3 may be synthesized by acylation of the amine of Formula 1-1 using the acid chloride of W, i.e.,  $\text{WCOCl}$  or  $\text{W}(\text{CH}_2)_j\text{COCl}$  where j is an integer from 1 to 3, in a solvent such as  $\text{CH}_2\text{Cl}_2$  and a suitable tertiary amine such as triethylamine, at room temperature. Again, the K' amine and the acid chloride carbon attached to W together form K in the product.

This method also provides an alternative path to the compounds of Formula 1-2 by reduction of the amide of Formula 1-3 using borane-tetrahydrofuran (THF) complex, in THF as shown in Scheme 1, Step E, at elevated temperature in an inert atmosphere.

Compounds of Formula 1-4 in Scheme 1 where K comprises a ureido moiety may be synthesized by urea formation between the compound of Formula 1-1 and a substituted aryl isocyanate or aryl carbamate, as shown in Scheme 1, Step F, in a suitable solvent and a suitable tertiary amine such as triethylamine and N-methylmorpholine, at room temperature in an inert atmosphere. The ureido moiety comprising K is formed between the K' amine and the

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isocyanate (or isothiocyanate) attached to W, or between K'' and the carbamate derivative of W. Alternatively, compounds containing a thiourea moiety instead of a urea moiety may be synthesized similarly by simply replacing the aryl isocyanate described above with an aryl isothiocyanate.

Suitable aryl carbamates may be of the form  $WCO_2Ar'$  where W is for example



15

and  $Ar'$  may be for example 4-nitrophenyl.

#### Synthesis of the compounds of Table 1

As an illustrative example of the synthesis of the compounds shown in Table 1, the synthesis of Example 1 from Table 1, is provided below:

**N-[6{((Naphthalen-2-ylmethyl)-amino)-hexyl}-2-nitrobenzenesulfonamide**

#### 25 Step A, Scheme 1

**[6-(2-Nitrobenzenesulfonylamino)-hexyl]-carbamic acid t-butyl ester:**

To a stirred solution of N-Boc 1, 6-diaminohexane hydrochloride (1.51 g, 6 mmol) and triethyl amine (1.31 g, 13 mmol) in 50 mL methylene chloride was added 2-Nitrobenzenesulfonyl chloride (1.326 g, 6 mmol). The reaction mixture was stirred for 6 h at room temperature, quenched with brine, and extracted with methylene chloride (2x50 mL). The organic layer was washed with brine (a saturated solution of sodium chloride in water, unless

otherwise specified), dried over anhydrous sodium sulfate, and concentrated in vacuo to yield the titled compound as yellow oil (2.1 g, 87%).

5      **Step B, Scheme 1**

**N-(6-Aminohexyl)-2-nitrobenzenesulfonamideHydrochloride:**

To a stirred solution of [6-(2-Nitrobenzenesulfonylamino)-hexyl]-carbamic acid t-butyl ester (2.0 g, 4.9 mmol) in 25 mL of methylene chloride at room temperature was added 3 mL of saturated HCl solution in ethyl acetate and stirred for 4 h. The precipitated solid was filtered to yield the titled compound as white solid (1.58 g, 95%); mp 161-162 °C.

15      **Step C, Scheme 1**

**N-[6{(Naphthalen-2-ylmethyl)-amino}-hexyl]-2-nitrobenzenesulfonamide:**

A mixture of N-(6-Aminohexyl)-2-nitrobenzenesulfonamide hydrochloride (0.67 g, 2.0 mmol) and 2-naphthaldehyde (0.32 g, 2.1 mmol) in 75 mL of toluene was refluxed using a Dean Stark trap for 20 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in ethanol (40 mL) and sodium borohydride (0.020 g, 6.0 mmol) was added. After the reaction was complete (6 h), the solvent was evaporated and residue taken up in 30 mL of saturated sodium chloride solution and extracted with ethyl acetate (3x40mL), washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated to afford an oil. The oil was flash chromatographed over silica gel to afford the titled compound (0.16 g, 37%) which was converted into hydrochloride salt (mp 169°C).

An example of the use of the alternative path to the compounds of Formula 1-2 by reduction of the amide of Formula 1-3 using borane-THF complex as previously

described for Scheme 1, Step E, is provided for Example 15 of Table 1, as follows:

5     **N-[6{(1, 2, 3, 4-tetrahydronaphthalen-2-ylmethyl)-amino}-hexyl]-2-aminobenzenesulfonamide**

To a solution of 1, 2, 3, 4-tetrahydro-2-naphthalencarboxylic acid[6-(2-nitrobenzenesulfonylamino)-hexyl]-amide (0.090 g, 0.19 mmol) in tetrahydrofuran (5 mL) cooled to 0 °C was added 2 mL 1M solution of borane:THF  
10     complex and the reaction mixture was refluxed for 12h. The reaction mixture was cooled in an ice bath and quenched with 2 mL of 1N HCl. The reaction mixture was neutralized with 10% aqueous sodium hydroxide solution and extracted with ethyl acetate (3x25 mL). The organic phase was washed  
15     with brine, dried over sodium sulfate, and evaporated in vacuo to afford an oil which was purified by preparative TLC to afford the titled compound (0.06 g, 70%); hydrochloride salt mp (162-163 °C).

20     Using appropriately substituted starting materials, the other Examples shown in Table 1 were synthesized as described above, with the exception of Example 52. The compound of Example 52 in Table 1 was synthesized similarly, except that before deprotection of the amine of  
25     Formula 1-1 in Scheme 1 Step B, the sulfonyl nitrogen was alkylated with methyl iodide in dimethylformamide at room temperature to afford the N-methylated sulfonamide product (Sato et al., 1995), which was subsequently deprotected as in Scheme 1, Step B, for use in the remainder of Scheme 1.  
30     Other n-alkyl derivatives may be prepared similarly, using an n-alkyl halide in an inert solvent such as dimethylformamide as described above.

Table 1

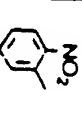







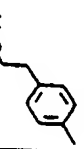

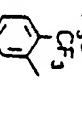

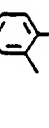

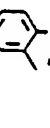

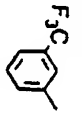

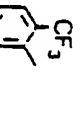

No.	Ar	X	R1	L	K	W	mp	Analysis
1		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		169	C <sub>23</sub> H <sub>28</sub> N <sub>3</sub> O <sub>4</sub> S + HCl + 0.05 CHCl <sub>3</sub>
2		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		174	C <sub>27</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub> S + HCl
3		-	H	-(CH <sub>2</sub> ) <sub>4</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		194.5	C <sub>28</sub> H <sub>28</sub> N <sub>2</sub> O <sub>4</sub> S + HCl + 0.04 CHCl <sub>3</sub>
4		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		190.1	C <sub>27</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub> S + HCl
5		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		149-50	
6		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		158	C <sub>24</sub> H <sub>27</sub> N <sub>2</sub> O <sub>2</sub> SF <sub>3</sub> + HCl
7		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		111-12	
8		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		139	C <sub>21</sub> H <sub>20</sub> N <sub>3</sub> O <sub>6</sub> S + HCl + 0.1H <sub>2</sub> O
9		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		172.4	C <sub>24</sub> H <sub>27</sub> N <sub>2</sub> O <sub>2</sub> SF <sub>3</sub> + HCl
10		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		167	C <sub>24</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub> SF <sub>3</sub> + HCl

Table: 1 (cont)










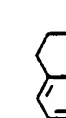

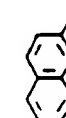








No.	Ar	X	R <sub>1</sub>	L	K	W	mp	Analysis
11		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		139-40	C <sub>27</sub> H <sub>31</sub> N <sub>2</sub> O <sub>2</sub> S + HCl
12		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		194-6	C <sub>25</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub> S + HCl
13		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		119-20	C <sub>25</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub> S + HCl
14		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		120-1	C <sub>24</sub> H <sub>30</sub> N <sub>2</sub> O <sub>3</sub> S + HCl
15		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		162-63	C <sub>23</sub> H <sub>28</sub> N <sub>3</sub> O <sub>2</sub> S + 2.0 HCl
16		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		141	C <sub>24</sub> H <sub>30</sub> N <sub>3</sub> O <sub>4</sub> S + HCl + 0.1 CH <sub>2</sub> Cl <sub>2</sub>
17		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		183-6	C <sub>23</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub> S + HCl
18		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		181-4	C <sub>26</sub> H <sub>31</sub> N <sub>3</sub> O <sub>4</sub> S + HCl
19		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		158	C <sub>29</sub> H <sub>34</sub> N <sub>2</sub> O <sub>2</sub> S + HCl
20		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		145-6	C <sub>29</sub> H <sub>34</sub> N <sub>2</sub> O <sub>2</sub> S + HCl

Table 1 (cont)

No.	Ar	X	R1	L	K	W	mp	Analysis
21		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		117-20	C <sub>26</sub> H <sub>30</sub> N <sub>3</sub> O <sub>4</sub> SF <sub>3</sub> + HCl
22		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		153-5	C <sub>25</sub> H <sub>33</sub> N <sub>3</sub> O <sub>2</sub> SF <sub>3</sub> + HCl
23		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		166-8	C <sub>25</sub> H <sub>33</sub> N <sub>3</sub> O <sub>2</sub> S + 2.0 HCl
24		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		120-2	C <sub>26</sub> H <sub>34</sub> N <sub>2</sub> O <sub>3</sub> S + HCl + 0.05 CHCl <sub>3</sub>
25		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		134-6	C <sub>25</sub> H <sub>35</sub> N <sub>3</sub> O <sub>4</sub> S + HCl
26		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		129-31	C <sub>25</sub> H <sub>37</sub> N <sub>3</sub> O <sub>2</sub> S + 2.0 HCl
27		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		113-4	C <sub>26</sub> H <sub>38</sub> N <sub>3</sub> O <sub>3</sub> S + HCl + 0.1 CHCl <sub>3</sub>
28		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		250-1	C <sub>29</sub> H <sub>32</sub> N <sub>3</sub> O <sub>2</sub> S + HCl
29		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		195	C <sub>29</sub> H <sub>31</sub> N <sub>2</sub> O <sub>2</sub> S + HCl + 0.25 H <sub>2</sub> O
30		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCH <sub>2</sub>		172	C <sub>29</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S + HCl + 0.25 CH <sub>2</sub> Cl <sub>2</sub>



Table I(cont)


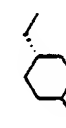
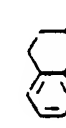
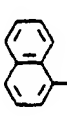



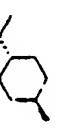

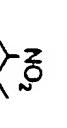
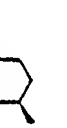
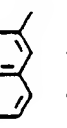
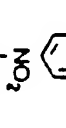
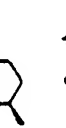
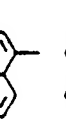



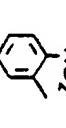


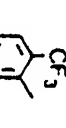


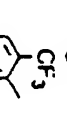



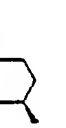
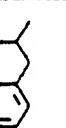


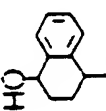



No.	Ar	X	R <sub>1</sub>	L	K	W	mp	Analysis
31		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		210	C <sub>28</sub> H <sub>36</sub> N <sub>2</sub> O <sub>2</sub> S + HCl
32		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		220	C <sub>28</sub> H <sub>36</sub> N <sub>2</sub> O <sub>2</sub> S + HCl + 0.15 CH <sub>2</sub> Cl <sub>2</sub>
33		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		201	C <sub>28</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S + HCl + 0.3 CHCl <sub>3</sub>
34		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		194-5	C <sub>25</sub> H <sub>28</sub> N <sub>3</sub> O <sub>4</sub> S + HCl + 0.1 CHCl <sub>3</sub>
35		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		Hygroscopic	C <sub>25</sub> H <sub>28</sub> N <sub>3</sub> O <sub>4</sub> S + HCl + 0.2 C <sub>6</sub> H <sub>14</sub>
36		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		200-2	C <sub>25</sub> H <sub>33</sub> N <sub>3</sub> O <sub>4</sub> S + HCl
37		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		216-7	C <sub>26</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub> SF <sub>3</sub> + HCl
38		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		171-4	C <sub>26</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub> SF <sub>3</sub> + HCl + 0.075 CHCl <sub>3</sub>
39		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		75-8	C <sub>26</sub> H <sub>33</sub> N <sub>2</sub> O <sub>2</sub> SF <sub>3</sub> + HCl + 0.05 CHCl <sub>3</sub>
40		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		175-7	C <sub>26</sub> H <sub>35</sub> N <sub>3</sub> O <sub>2</sub> S + 2 HCl + 0.8 Et <sub>2</sub> O

Table 1(cont)

No.	Ar	X	R1	L	K	W	mp	Analysis
41		-	H		$\text{CH}_2\text{NHCH}_2$		Hygroscopic	$\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_2\text{S}$ + HCl
42		-	H		$\text{CH}_2\text{NHCH}_2$		118-20	$\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_2\text{S}$ + 2.6 HCl
43		-	H		$\text{CH}_2\text{NHCH}_2$		115 dec	$\text{C}_{23}\text{H}_{31}\text{N}_6\text{O}_4\text{S}$ + 2.4 HCl
44		-	H		$\text{CH}_2\text{NHCH}_2$		89 dec	$\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_4\text{S}$ + 2 HCl
45		-	H		$\text{CH}_2\text{NHCH}_2$		104-6	$\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_4\text{S}$ + 2 HCl + 0.25 $\text{CHCl}_3$
46		-	H		$\text{CH}_2\text{NHCH}_2$		78-80	$\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_4\text{S}$ + 2 HCl + 0.65 $\text{CHCl}_3$
47		-	H		$\text{CH}_2\text{NHCH}_2$		249-51	$\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_6\text{S}$ + HCl + 0.1 $\text{CHCl}_3$
48		-	H		$\text{CH}_2\text{NHCH}_2$		220-21	$\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_6\text{S}$ + HCl + 0.05 $\text{CHCl}_3$
49		-	H		$\text{CH}_2\text{NHCH}_2$		62-5	$\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_6\text{S}$ + HCl + 0.5 $\text{CHCl}_3$
50		-	H		$\text{CH}_2\text{NHCH}_2$		196-7	$\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_5\text{S}$ + HCl

Table 1 (cont)

No.	Ar	X	R <sub>1</sub>	L	K	W	m.p.	Analysis
51		-	H		CH <sub>2</sub> NHCH <sub>2</sub>		57	C <sub>25</sub> H <sub>33</sub> N <sub>3</sub> O <sub>5</sub> S + HCl + 0.13 CHCl <sub>3</sub>
52		-	CH <sub>3</sub>		CH <sub>2</sub> NHCH <sub>2</sub>		235-6	C <sub>30</sub> H <sub>34</sub> N <sub>2</sub> O <sub>2</sub> S + HCl

### Synthesis of the compounds of Table 2

As an illustrative example of the synthesis of the compounds shown in Table 2 as shown in Scheme 1, Step D, the synthesis of Example 53 from Table 2, is provided below:

1, 2, 3, 4-Tetrahydro-2-naphthalencarboxylic acid[6-(2-nitrobenzenesulfonylamino)-hexyl]-amide

#### Step D, Scheme 1

1, 2, 3, 4-Tetrahydro-2-naphthalencarboxylic acid[6-(2-nitrobenzenesulfonylamino)-hexyl]-amide:

A mixture of N-(6-aminohexyl)-2-nitrobenzenesulfonamide hydrochloride (0.2 g, 0.58 mmol), EDC (0.252 g, 1.31 mmol), and DMAP (0.14 g, 1.21 mmol) in methylene chloride (30 mL) was stirred at room temperature for 0.5h. 1, 2, 3, 4-tetrahydronaphthalen-2-carboxylic acid (0.114 g, 0.65 mmol) was added to the reaction mixture and stirred at room temperature until the completion of the reaction (determined by TLC). The reaction mixture was washed with saturated ammonium chloride (3x30 mL), dried over sodium sulfate and concentrated in vacuo. The residue was flash chromatographed over silica gel to afford an oil (0.25 g, 93%).

Other compounds of Formula 1-3, as shown in Table 2, were synthesized using the methods described above, except for Examples 59 and 63. Example 59 was synthesized as shown in Scheme 1, except for the use of sulfamyl chloride starting material Ar-NH-SO<sub>2</sub>Cl instead of the sulfonyl chloride Ar-SO<sub>2</sub>Cl (Benson and Spillane, Chem. Rev. 80:151-186, 1980).

Example 63 of Table 2 was synthesized from the compound of Example 53 of Table 2 by reduction of the aryl nitro moiety using tin chloride in HCl/Acetic acid/H<sub>2</sub>O at room

temperature, to afford the amino aryl derivative (such as in Example 56, Table 2), which was then sulfonylated with alkyl sulfonyl chloride to afford the bis-sulfonylated compound of Example 63 as follows:

5

1, 2, 3, 4-Tetrahydro-2-naphthalencarboxylic acid[6-{2-(bismethanesulfonylamino)benzenesulfonylamino}}-hexyl]-amide

10 (a) 1, 2, 3, 4-Tetrahydro-2-naphthalencarboxylic acid[6-(2-aminobenzenesulfonylamino)-hexyl]-amide:

To a solution of 1, 2, 3, 4-Tetrahydro-2-naphthalencarboxylic acid[6-(2-nitrobenzenesulfonylamino)-hexyl]-amide (0.54 g, 1.17 mmol) in 5 mL of glacial acetic acid stirred at 0 °C was added a solution of tin chloride (1.32 g, 5.88 mmol) in 5 mL conc. HCl and 1 mL of water. The reaction mixture was warmed to room temperature and stirred for 3 h and poured over crushed ice (50 g). The reaction mixture was neutralized with 10% sodium hydroxide and extracted with chloroform (5x50 mL), dried over sodium sulfate and concentrated to afford yellow oil (0.48 g, 95%).

25 (b) 1, 2, 3, 4-Tetrahydro-2-naphthalencarboxylic acid[6-{2-(bismethanesulfonylamino)benzenesulfonylamino}}-hexyl]-amide:

To a solution of 1, 2, 3, 4-tetrahydro-2-naphthalencarboxylic acid[6-(2-aminobenzenesulfonylamino)-hexyl]-amide (0.075 g, 0.17 mmol) in chloroform (3 mL), and triethylamine (0.1 g, 1 mmol) stirred at 0 °C was added methane sulfonyl chloride (30 mL, 0.35 mmol) and the reaction mixture was stirred at room temperature for 3 h. Solvent was evaporated and purifications by preparative TLC afforded the titled compound as white solid (0.1 g, 97%); mp 70 °C.

35

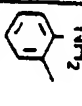


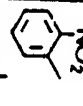
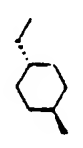
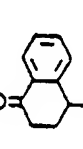
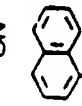
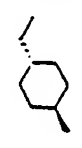
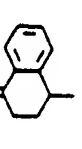
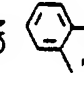
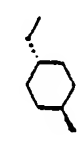
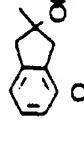
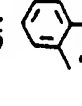
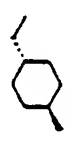

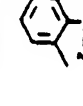
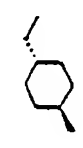

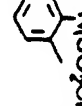
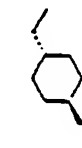

-70-

The amine of Example 56, Table 2, further may be acylated in the same manner as above in Example 63 but using suitable alkyl acyl chlorides instead of an alkyl sulfonyl chloride.

Table 2

No.	Ar	X	R <sub>1</sub>	L	K	W	mp	Analysis
53		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		Oil	C <sub>23</sub> H <sub>26</sub> N <sub>3</sub> O <sub>5</sub> S + 0.35 CH <sub>2</sub> Cl <sub>2</sub>
54		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		Oil	C <sub>24</sub> H <sub>32</sub> N <sub>2</sub> O <sub>4</sub> S + 0.6 CHCl <sub>3</sub>
55		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		Oil	C <sub>24</sub> H <sub>28</sub> N <sub>3</sub> O <sub>5</sub> SF <sub>3</sub> + 0.2 C <sub>6</sub> H <sub>14</sub>
56		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		72-4	C <sub>23</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub> S + 0.25 CH <sub>2</sub> Cl <sub>2</sub>
57		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		132	C <sub>23</sub> H <sub>28</sub> N <sub>4</sub> O <sub>5</sub> SF <sub>3</sub> + HCl + 0.05 CHCl <sub>3</sub>
58		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		98	C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>5</sub> S + HCl + 0.1 CHCl <sub>3</sub>
59		NH	H	-(CH <sub>2</sub> ) <sub>4</sub> -	CH <sub>2</sub> NHCO		Oil	C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>6</sub> S + 0.35 CH <sub>2</sub> Cl <sub>2</sub>
60		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		Oil	C <sub>23</sub> H <sub>25</sub> N <sub>3</sub> O <sub>5</sub> S
61		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		105	C <sub>23</sub> H <sub>25</sub> N <sub>3</sub> O <sub>5</sub> S
62		-	H	-(CH <sub>2</sub> ) <sub>7</sub> -	CH <sub>2</sub> NHCO		Oil	C <sub>25</sub> H <sub>33</sub> N <sub>3</sub> O <sub>5</sub> S + 0.15 CHCl <sub>3</sub>
63		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		70	C <sub>25</sub> H <sub>35</sub> N <sub>3</sub> O <sub>7</sub> S <sub>3</sub>

Table 2 (cont)

No.	Ar	X	R <sub>1</sub>	L	K	W	mp	Analysis
64		-	H		CH <sub>2</sub> NHCO		194-7	C <sub>25</sub> H <sub>33</sub> N <sub>3</sub> O <sub>3</sub> S + HCl + 0.2 CHCl <sub>3</sub>
65		-	H		CH <sub>2</sub> NHCO		78-80	C <sub>25</sub> H <sub>38</sub> N <sub>3</sub> O <sub>6</sub> S + HCl + 0.3 CHCl <sub>3</sub>
66		-	H		CH <sub>2</sub> NHCO		86-87	C <sub>29</sub> H <sub>32</sub> N <sub>2</sub> O <sub>4</sub> S + HCl + 0.35 CHCl <sub>3</sub>
67		-	H		CH <sub>2</sub> NHCO		59-61	C <sub>29</sub> H <sub>32</sub> N <sub>2</sub> O <sub>4</sub> S + 0.2 CHCl <sub>3</sub>
68		-	H		CH <sub>2</sub> NHCO		150-3	C <sub>23</sub> H <sub>25</sub> N <sub>5</sub> O <sub>5</sub> S + 0.25 CHCl <sub>3</sub>
69		-	H		CH <sub>2</sub> NHCO		62-4	C <sub>24</sub> H <sub>28</sub> N <sub>4</sub> O <sub>5</sub> S + 0.3 CHCl <sub>3</sub>
70		-	H		CH <sub>2</sub> NHCO		85-7	C <sub>27</sub> H <sub>37</sub> N <sub>3</sub> O <sub>7</sub> S <sub>3</sub> + 0.25 CHCl <sub>3</sub>



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**Synthesis of the compounds of Table 3**

As an illustrative example of the synthesis of the compounds shown in Table 3 and Table 3a, as shown in Scheme 1, Step F, the synthesis of Example 71 from Table 3, is provided below:

**Synthesis of Naphthalene-1-sulfonic acid{6-[3-(1-naphthyl)-uriedo]-hexyl}-amide****10 Step F, Scheme 1**

To a solution of N-(6-aminohexyl)-1-naphthalenesulfonamide hydrochloride(0.1 g, 0.29 mmol) in 3 mL dimethylformamide and 50 mL N-methyl morpholine was added 1-naphthalene isocyanate(68  $\mu$ L, 0.4 mmol). The reaction mixture was stirred at room temperature for 6 h. Solvent was evaporated in vacuo and residue was purified by preparative TLC to afford white solid(110 mg, 79%);mp 105-106 °C.

20 An example of the synthesis of a compound of Formula 1-4 in Scheme 1, using an aryl carbamate as previously described, is provided for Example 74 of Table 3, as follows:

**25 3, 4-Dihydroquinoline-1-carboxylic acid[6-(2-trifluoromethylbenzenesulfonylamino)-hexyl]amide****(a) 3, 4-Dihydro-2H-quinoline-1-carboxylic acid 4-nitrophenyl ester**

To a solution of tetrahydroisoquinoline (3.99 g, 30 mmol) in triethyl amine(6 g, 60 mmol) and dichloromethane(150 mL) cooled in ice bath was added p-nitrophenyl chloroformate (6.06 g, 30 mmol) drop wise over a period of 1h. The reaction mixture was stirred at room temperature for 3h and then washed with water (3x100 mL), dried over sodium sulfate and concentrated to afford an oil which was

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trituated with ether:hexane to afford the titled compound as yellow solid (5.9 g, 65%).

(b) 3, 4-Dihydroquinoline-1-carboxylic acid[6-(2-trifluoromethylbenzenesulfonylamino)-hexyl]amide:

To a solution of N-(6-Aminohexyl)-2-trifluoromethylbenzene sulfonamide Hydrochloride (0.1 g, 0.27 mmol) dimethyl formamide (3mL) and triethylamine (0.1 g, 1mmol) was added 3, 4-Dihydro-2H-quinoline-1-carboxylic acid 4-nitrophenyl ester (0.09 g, 0.3 mmol) and the reaction mixture was stirred at room temperature for 4h. Solvent was evaporated and purification by preparative TLC afford the titled compound as an oil (0.08g, 61 %).

15 **Synthesis of the compounds of Table 3a**

As illustrative examples of the synthesis of the compounds of Table 3a, as shown in Scheme 1, Step F, the syntheses of Examples 80-82 and 87 is provided below:

20 **Example 80**

**1-[1-(Naphthalene-1-sulfonyl)-piperidine-4-ylmethyl]-3-naphthalene-1-ylmethylthiourea**

**1-Naphthalene-1-ylmethyl-3-piperidine-4-ylmethylthiourea**

To a solution of 1-naphthalenemethylisothiocyanate (2.8 g, 13.6 mmol) in 100 ml of MeOH-THF solution (1:1 mixture) was added 4-aminomethylpiperidine (3.1 ml, 27.0 mmol) in a portion and the resulting solution was stirred at reflux for 12 h. The reaction mixture was concentrated in vacuo, yielding oily mixture which was subjected to column chromatography (10% MeOH/CHCl<sub>3</sub>) to yield 2.3 g (48%) of the desired product as an oil.

**1-[1-(Naphthalene-1-sulfonyl)-piperidine-4-ylmethyl]-3-naphthalene-1-ylmethylthiourea**

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To a solution of the amine (0.34 g, 1.1 mmol) in 10 ml of pyridine was added 1-naphthalenesulfonyl chloride (0.30 ml, 1.3 mmol) in a portion and the resulting mixture was stirred at 25°C for 12 h. The reaction mixture was subjected to column chromatography (50% Hexane/EtOAc) to yield 0.21 g (38%) of the desired product as yellow solid, which was recrystallized from EtOAc to provide 0.15 g of the product as white solid: mp 83 - 85 °C; Anal. Cal. For  $C_{28}H_{29}N_3O_2S_2$  requires C, 66.77; H, 5.80; N, 8.34. Found: C, 64.32; H, 5.89; N, 8.27.

**Example 81**

**2-methyl-1-[1-(naphthalene-1-sulfonyl)piperidine-4-ylmethyl]-3-naphthalene-1-ylmethylisothiurea**

To a solution of the thiourea of Example 80 (0.11 g, 0.32 mmol) in MeOH was added MeI (0.5 ml, 8.1 mmol) in a portion and the resulting mixture was stirred at 25°C for 12 h. The reaction mixture was concentrated in vacuo, yielding a solid which was recrystallized from EtOH to yield 0.11 g (53%) of the desired product as white solid: mp 111 - 113°C; Anal. Cal. For  $C_{29}H_{31}N_3O_2S_2$ . 1.0 HI requires C, 54.04; H, 4.89; N, 6.52. Found: C, 52.97; H, 5.01; N, 6.47.

**Example 82**

**1-[1-(Naphthalene-1-sulfonyl)-piperidine-4-ylmethyl]-3-naphthalene-1-ylmethylurea**

**1-Naphthalene-1-ylmethyl-3-piperidine-4-ylmethylurea**

To a solution of 1-naphthalenemethylcyanate (1.1 g, 6.0 mmol) in 50 ml of  $CHCl_3$  was added 4-aminomethylpiperidine (0.9 ml, 7.8 mmol) in a portion and the resulting solution was stirred at reflux for 12 h. The reaction mixture was concentrated in vacuo, yielding oily mixture which was purified on column chromatography (5% MeOH/ $CHCl_3$ ) to yield

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the desired product 1.6 g (89%) of the desired product as an oil.

5      **1-[1-(Naphthalene-1-sulfonyl)-piperidine-4-ylmethyl]-3-naphthalene-1-ylmethylurea**

To a solution of the amine (0.60 g, 2.0 mmol) in 30 ml of pyridine was added 1-naphthalenesulfonyl chloride (0.60 ml, 2.7 mmol) in a portion and the resulting mixture was stirred at 25°C for 12h. The reaction mixture was subjected to column chromatography (CHCl<sub>3</sub>, neat) to yield 10      0.63 g (65%) of the desired product as light yellow solid, which was recrystallized from EtOAc to provide 0.37 g of the product as white solid: mp 103 - 104°C; Anal. Cal. For C<sub>28</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>S requires C, 64.97; H, 5.99; N, 8.62. Found: C, 15      66.03; H, 5.83; N, 8.49.

**Example 87**

20      **1-Naphthalene-1-ylmethyl-3-[1-(2-trifluoromethyl-benzenesulfonyl)-pyrrolidin-3-yl]-urea**

1-(Naphthalene-1-sulfonyl)-pyrrolidin-3-ylamine  
To a solution of 1-naphthalenesulfonyl chloride (1.0 g, 5.4 mmol) in 50 ml of CH<sub>2</sub>Cl<sub>2</sub> with 2 ml of trimethylamine was added 3-t-butoxycarbonylpyrrolidine (1.5 g, 6.5 mmol) 25      in a portion and the resulting solution was stirred at reflux for 48 h. Reaction mixture was concentrated in vacuo, yielding oily mixture which was partitioned between 100 ml of EtOAc and NaHCO<sub>3</sub> sat'd aqueous solution. Organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to provide an oil, which was 30      redissolved in 20 ml of CH<sub>2</sub>Cl<sub>2</sub>. Toward this solution was added 1 ml of trifluoroacetic acid and the resulting solution was stirred for 2 h at 25°C. Reaction mixture was concentrated in vacuo, providing a brown oil, which 35      was dissolved in EtOAc and washed with aqueous NaOH.

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Organic layer was concentrated in vacuo to yield an oil which was subjected to column chromatography (30% MeOH/CHCl<sub>3</sub>) to provide 0.17 g (23%) of the desired product.

5

**1-Naphthalene-1-ylmethyl-3-[1-(2-trifluoromethyl-benzenesulfonyl)-pyrrolidin-3-yl]-urea**

The amine (37 mg, 0.12 mmol) and naphthalene-1-ylmethyl-carbamic acid 4-nitro-phenyl ester (61 mg, 0.19 mmol) in 10 5 ml of CH<sub>2</sub>Cl<sub>2</sub> was stirred at 25°C for 12 h. The reaction mixture was subjected to column chromatography (2% MeOH/CHCl<sub>3</sub>) to yield 42 mg (74%) of the desired product as light yellow solid: mp 117 - 119 °C; Anal. Cal. For C<sub>23</sub>H<sub>22</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S requires C, 57.85; H, 4.64; N, 8.80. 15 Found: C, 56.16; H, 4.71; N, 8.67.

Additional compounds may be synthesized by substitution of appropriate starting materials, and are not intended to be limited to those compounds shown in Table 3a.

20

Other compounds of Formula 1-4, as shown in Table 3 and Table 3a, were synthesized using the methods described above, using appropriately substituted starting materials.

Table 3






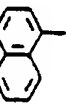

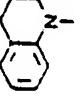
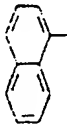
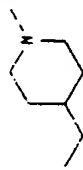
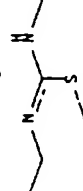
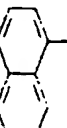
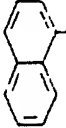
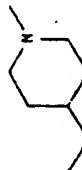
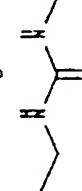


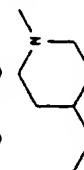
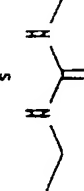

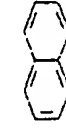
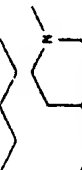
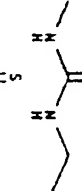
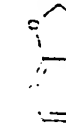
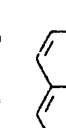

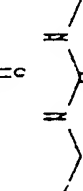
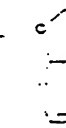

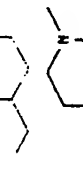
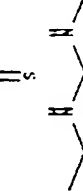
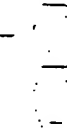
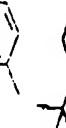
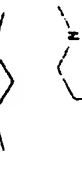
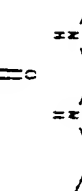
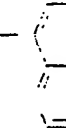

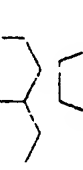
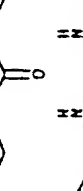
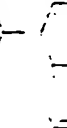
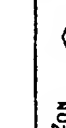
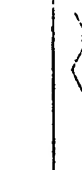
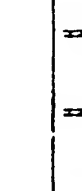
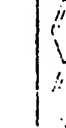
No.	Ar	X	R1	L	K	W	mp	Analysis
71		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>12</sub> NHCONH		105-06	C <sub>27</sub> H <sub>28</sub> N <sub>3</sub> O <sub>3</sub> S
72		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCONH		115	C <sub>23</sub> H <sub>28</sub> N <sub>4</sub> O <sub>6</sub> S
73		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCONH		Oil	C <sub>24</sub> H <sub>28</sub> N <sub>3</sub> O <sub>4</sub> S + 0.5 CHCl <sub>3</sub>
74		-	H	-(CH <sub>2</sub> ) <sub>5</sub> -	CH <sub>2</sub> NHCO		Oil	C <sub>23</sub> H <sub>28</sub> N <sub>3</sub> O <sub>3</sub> S

Table 3a

No	Ar	X	L	K	W	mp	
81		.				111-113	$C_{26}H_{21}N_3O_2S + HI$
80		.				83-85	$C_{26}H_{21}N_3O_2S$
82		.				104-106	$C_{26}H_{21}N_3O_2S$
83		.				176-178	$C_{25}H_{21}N_3O_4S$
84		.				199-201	$C_{25}H_{21}N_3O_4S$
85		.				94-97	$C_{25}H_{26}F_6N_3O_5S$
86		.				88-90	$C_{24}H_{26}F_6N_3O_5S_2$
87		.				117-119	$C_{23}H_{22}F_6N_3O_5S$
88		.				162-164	$C_{24}H_{26}N_3O_5S$

**Synthesis of compounds of Scheme 2**

Compounds in which L is substituted may be produced according to Scheme 2. The carbobenzyloxy-protected amino acid derivative of L may be esterified by thionyl chloride and methanol as shown in Scheme 2, Step A, and the ester subsequently reduced by diisobutylaluminum hydride in THF as shown in Scheme 2, Step B, at -78 °C, to yield alcohol, which is then oxidized by pyridinium chlorochromate in Scheme 2, Step C, in a suitable solvent such as CH<sub>2</sub>Cl<sub>2</sub>, to afford an aldehyde of Formula 2-1. The aldehyde may be treated with ammonia, and then trimethylsilylcyanide (Chakraborty, et al. Tet. Lett. 32(51):7597-7600, 1991) as shown in Scheme 2, Step D, in a suitable solvent such as methanol, to yield the compound of Formula 2-2. The compound of Formula 2-2 may be subjected to sulfonylation as described above in Scheme 1, Step A, to yield the compound of Formula 2-3. The cyano moiety of the compound of Formula 2-3 may be esterified and deblocked to afford compounds of Formula 2-4; or if desired, the compound of Formula 2-3 may be further reduced, or hydrolyzed as appropriate to yield substituted compounds other than those shown in Formula 2-5, which compounds may be further used in any of Steps C, D, E, or F of Scheme 1.

An example of the synthesis of a compound of Formula 2-5 is the synthesis of compound 79:

**7 - [ ( N a p h t h a l e n - 2 - y l m e t h y l ) - a m i n o ] - 2 - ( 2 - n i t r o b e n z e n e s u l f o n y l a m i n o ) - h e p t a n o i c a c i d m e t h y l e s t e r**

**(a) Step A, Scheme 2****6-Benzyloxycarbonylamino-hexanoic Acid Methyl Ester:**

To a solution of 6-benzyloxycarbonylamino-hexanoic acid (10 g, 38 mmol) in methanol (200 mL) at room temperature was added thionyl chloride (11 g, 95 mmol). The reaction



mixture was then refluxed for 16 h. The solvent was concentrated in vacuo, the residue was dissolved in ethyl acetate (200 mL) and washed with brine (3x150 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography (silica, 14% ethyl acetate in hexane) to afford the titled compound (6.2 g, 58%), a colorless liquid.

10 (b) Step B, Scheme 2

(6-Hydroxyhexyl)-carbamic acid benzyl ester:

To a solution of diisobutylaluminum hydride (49 mL, 1.5 M in toluene) in THF (150 mL) cooled to -78 °C was added a solution of 6-benzyloxycarbonylamino-hexanoic acid methyl ester (10 g, 37 mmol) in THF (100 mL). The reaction mixture was stirred for 4 h and methanol (2.5 mL) was added carefully at -78 to -75 °C. After 2 h, the mixture was poured to 250 mL of 1 N HCl solution cooled in ice-bath, extracted with ethyl acetate (300 mL), washed with brine (3x100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography (silica, 50% ethyl acetate in hexane) to yield the titled compound (7.1 g, 80%); white solid, mp 67-68 °C.

25

(c) Step C, Scheme 2

(6-Oxy-hexyl)-carbamic acid benzyl ester:

To a suspension of pyridinium chlorochromate (9.2 g, 43 mmol) and celite (37 g) in methylene chloride (400 mL) was added (6-hydroxyhexyl)-carbamic acid benzyl ester (7.1 g, 24 mmol). The mixture was stirred for 3 h and dry ethyl ether (500 mL) was added to it. The mixture was stirred for additional 0.5 h, filtered through a pad of celite and concentrated in vacuo. The residue was purified by flash column chromatography (silica, 10-25% ethyl acetate in

35

hexane) to yield the titled compound (4.8 g, 79%); colorless light oil.

(d) Step D, Scheme 2

5 (6-Amino-6-cyano-hexyl)-carbamic acid benzyl ester:

Ammonia was bubbled through a stirred solution of (6-oxy-hexyl)-carbamic acid benzyl ester (6.0 g, 24 mmol) in methanol (200 mL) for 2 h and TMSCN (2.9 g, 28 mmol) was added dropwise. The reaction mixture was stirred for 24 h.  
10 The solvent was evaporated in vacuo. The residue was purified by flash column chromatography (silica, 90-100% ethyl acetate in hexane) to yield the titled compound (4.3 g, 65%); light yellow oil.

15 (e) (Step A, Scheme 1)

(6-Benzenesulfonylamino-6-cyano-hexyl)-carbamic acid benzyl ester:

Using the general procedure described in step A of scheme 1, (6-amino-6-cyano-hexyl)-carbamic acid benzyl ester (2.8  
20 g, 10 mmol) was sulfonylated with 2-nitrobenzenesulfonyl chloride (2.5 g, 11 mmol) at 0 °C to yield the titled compound (1.7 g, 36%); yellow oil.

(f) Step E, Scheme 2

25 7-Amino-2-nitrobenzenesulfonylamino-heptanoic acid methyl ester:

Dry HCl gas was bubbled to a stirred solution of (6-benzenesulfonylamino-6-cyano-hexyl)-carbamic acid benzyl ester (0.58 g, 1.3 mmol) in dry methanol (50 mL) for 2h.  
30 The reaction mixture was cooled and solvent was evaporated in vacuo. Water (40 mL) was added to the reaction mixture and neutralized with 1 N NaOH to pH 9-10, extracted with ethyl acetate (4x100 mL), washed with brine (3x100 mL), dried over anhydrous magnesium sulfate, and  
35 concentrated in vacuo. The residue was purified by

-83-

preparative TLC (silica, 10% ammonia (2.0 M in methanol) in chloroform) to yield the titled compound (0.047 g, 10%); yellow thick oil.

5        (g) (Steps C, D, E, F, Scheme 1)

7 - [ (Naphthalen - 2 - ylmethyl) - amino] - 2 - (2 - nitrobenzenesulfonylamino) - heptanoic acid methyl ester:

Using the general procedure described in Steps C, D, E, and F of Scheme 1, 7-amino-2-nitrobenzenesulfonylamino-heptanoic acid methyl ester (0.060 g, 0.17 mmol) was  
10        reductively aminated with 2-naphthaldehyde (0.026 g, 0.017 mmol) to afford the titled compound (0.050 g, 60%); yellow oil.

15        Synthesis of compounds according to Scheme 3

Other compounds of the present invention may be synthesized according to Scheme 3. After protection of  $H_2N-L-COOH$  with Boc anhydride in  $CH_2Cl_2$ , as shown in Scheme 3, Step A, the protected amine may be amidated with W-K''' as in Scheme 3, Step B, where K''' is an alkylamino ester, using EDC and DMAP in a suitable solvent such as  $CH_2Cl_2$ , to yield compounds of Formula 3-1, where K''' and the carboxylic acid carbonyl of  $H_2N-L-COOH$  together form K. The compounds of Formula 3-1 may be deprotected using well  
25        known methods as shown in Scheme 3, Step C, and further sulfonylated with a sulfonyl halide of Ar, as shown in Scheme 3, Step D, in a suitable solvent such as  $CH_2Cl_2$  and a tertiary amine such as triethylamine, to form the compound of Formula 3-2. The compounds of Formula 3-2 may  
30        be reduced to yield the compounds of Formula 3-3, as shown in Scheme 3, Step E, using borane-tetrahydrofuran (THF) complex, in THF, at elevated temperature in an inert atmosphere.

A specific example of such a synthesis using Scheme 3 is provided below for Example 75 from Table 4:

5       trans-3-(4-Chloro-phenyl)-2-([4-(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl)-amino]-propionic acid methyl ester:

      (a) Step A, Scheme 3

      trans-4-(tert-Butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid:

10       To a solution of trans-4-(aminomethyl)cyclohexanecarboxylic acid (10 g, 57 mmol) in 1 N NaOH (110 mL) cooled to 0 °C was added a solution of di-tert-butyl dicarbonate (15 g, 69 mmol) in dioxane (50 mL). The reaction mixture was stirred at 0 °C for 12 h.  
15       The reaction mixture was neutralized by 1 N HCl solution to pH 3, extracted with ethyl ether (2x300 mL), washed with brine (2x300 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford the titled compound (16 g, 100%); white solid, mp 128-9 °C.

20

      (b) Step B, Scheme 3

      trans-2-[4-(tert-Butoxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino]3-(4-Chloro-phenyl)-propionic acid methyl ester:

25       Using the general procedure described for the preparation Step D, Scheme 1, trans-4-(tert-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (1.1 g, 4.0 mmol) was acylated with D,L-4-chlorophenylalanine methyl ester hydrochloride (1.0 g, 4.0 mmol) to afford the titled  
30       compound (1.9 g, 99%); white solid, mp 178-9 °C.

      (c) Step C, Scheme 3

      trans-2-[4-(Aminomethyl)-cyclohexanecarbonyl]-amino]3-(4-chloro-phenyl)-propionic acid methyl ester hydrochloride:

Using the general procedure described in step b scheme 1, trans-2-{[4-(tert-butoxycarbonylamino-methyl)-cyclohexanecarbonyl]-amino}3-(4-chloro-phenyl)-propionic acid methyl ester (1.8 g, 4.3 mmol) was deprotected using HCl in ethyl acetate to afford the titled compound; light yellow solid mp 146-9 °C.

(d) Step D, Scheme 3

trans-3-(4-Chloro-phenyl)-2-({[4-(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl}-amino)-propionic acid methyl ester:

Using the general procedure described in example A scheme 1, trans-2-[4-(aminomethyl-cyclohexanecarbonyl)-amino]3-(4-Chloro-phenyl)-propionic acid methyl ester hydrochloride (0.35 g, 0.86 mmol) was sulfonylated with 1-naphthalenesulfonyl chloride (0.42 g, 91%) to afford the titled ompound; white solid, mp 84-6 °C.

The compound of Example 77, Table 4, was synthesized from the above compound by borane-THF reduction as follows:





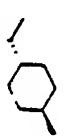

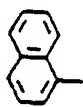
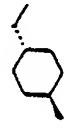
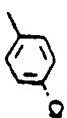

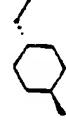

(e) Step E, Scheme 3

Naphthalene-1-sulfonic Acid trans-(4-{[2-(4-Chloro-phenyl)-1-hydroxymethyl-ethylamino]-methyl}-cyclohexylmethyl)-amide:

Using the general procedure described in Step H, Scheme 1, trans-3-(4-chloro-phenyl)-2-({[4-(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl}-amino)-propionic acid methyl ester (0.30 g, 0.55 mmol) was reduced by borane:THF complex (1.0 M in THF) to afford the titled compound; colorless oil.

Other compounds of Formula 3-3 or Formula 3-4, as shown in Table 4, where for example, K is substituted with an alcohol or ester, may also be synthesized using the methods of Scheme 3.

Table 4

No.	Ar	X	R <sub>1</sub>	L	K	W	mp	Analysis
75		-	H		$\text{PO}_2\text{CH}_3$ $\text{CONHCHCH}_2$		84-6	$\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_6\text{SCl}$ + 0.4 $\text{CHCl}_3$
76		-	H		$\text{PO}_2\text{CH}_3$ $\text{CONHCHCH}_2$		Oil	$\text{C}_{24}\text{H}_{28}\text{N}_3\text{O}_7\text{SCl}$ + 0.15 $\text{CHCl}_3$
77		-	H		$\text{CH}_2\text{OH}$ $\text{CH}_2\text{NHCHCH}_2$		223-3	$\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_5\text{SCl}$ + HCl
78		-	H		$\text{CH}_2\text{OH}$ $\text{CH}_2\text{NHCHCH}_2$		253-4	$\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_5\text{SCl}$ + HCl

**Synthesis of compounds 89 and 90**

The synthesis of compounds such as 89 and 90 may be accomplished by the method shown in Scheme 4, as described below:

5

**Example 89**

(a) 4-Oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid-(naphthalene-1-ylmethyl)-amide (Scheme 4, product 1):

A mixture of 1-naphthalenemethylamine (1.37 g, 7.2 mmol),  
10 4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid  
(1.13 g, 7.2 mmol) ECD (2.87 g, 15 mmol), and DMAP (1.83  
g, 15 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was stirred at room  
temperature. After 12 h, the reaction mixture was  
concentrated and the residue was purified by flash column  
15 chromatography (2-5% MeOH in  $\text{CH}_2\text{Cl}_2$  to yield the product  
(2.29 g, 97% light yellow solid, m.p. 155-156°C).

(b) 4-Cyano-4-trimethylsilanyloxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid-(naphthalene-1-ylmethyl)-amide (Scheme 4, product 2):

20 To a mixture of the product of step (a) (2.29 g, 6.95  
mmol) and a catalytic amount of  $\text{ZnI}_2$  in dry  $\text{CH}_2\text{Cl}_2$  (50 mL)  
at 0°C was added dropwise TMSCN (1.4 g, 1.87 mL, 14 mmol)  
under argon. The reaction mixture was warmed to room  
25 temperature and stirred for 24 h. After concentration of  
the reaction mixture, the residue was purified by flash  
column chromatography (2-5% MeOH in  $\text{CH}_2\text{Cl}_2$  to yield the  
product (1.6 g, 54%, 95% after recovering the product from  
(a); light yellow solid, m.p. 55-56°C).

30

(c) 1-Aminomethyl-4-[[[naphthalene-1-ylmethyl]-amino]-methyl]-1,2,3,4-tetrahydronaphthalene-1-ol (Scheme 4, product 3):

To a solution of the product of step (b) (1.4 g, 3.27  
35 mmol) in THF (30 mL) was added dropwise 25 mL of  $\text{BH}_3$ -THF

complex (1.0 M in THF) under argon. The reaction mixture was refluxed for 16 h. After cooling to 0°C, 6N HCl was added dropwise to the reaction mixture and the resultant mixture stirred for 24 h at room temperature. After cooling to 0°C, this mixture was neutralized by 1N NaOH to pH 7 to 8, extracted with ethyl acetate (100 mL), washed with water (60 mL x 2), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by flash column chromatography (2-5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to yield the product (0.30 g, 27%, light yellow solid).

(d) N-(1-hydroxy-4-{[(naphthalen-1-ylmethyl)-amino]-methyl}-1,2,3,4-tetrahydronaphthalen-1-ylmethyl-2-nitrobenzenesulfonamide (Scheme 4, product 4):

To a mixture of the product of step (c) (0.30 g, 0.866 mmol) and Et<sub>3</sub>N (0.35 g, 3.46 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0°C was added dropwise a solution of 2-nitrobenzenesulfonyl chloride (0.19 g, 0.866 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The reaction mixture was warmed to room temperature and stirred for 6 h. After concentration of the reaction mixture, the residue was purified by flash column chromatography (2-5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to yield the product (0.43 g, 93%, light yellow solid).

Example 90 (Scheme 4, product 5)

A mixture of the compound of Example 89 (0.35 g, 0.658 mmol) and TsOH (0.075 g, 0.395 mmol) in toluene was refluxed for 0.5 h. The reaction mixture was concentrated and purified by TLC chromatography (10% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to yield the product (0.217 g, 64%, light yellow solid, m.p. 53-54°C).

Pharmacological Evaluation of Compounds at Cloned Human Neuropeptide Y-type Receptors.



The pharmacologic properties of the compounds of the present invention were evaluated at the cloned human neuropeptide Y-type receptors Y1, Y2, Y4, and Y5, or in in vivo studies in rats, using the protocols described below.

5

## MATERIALS AND METHODS

### Cell Culture

10 COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37°C, 5% CO<sub>2</sub>. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 15 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37 °C, 5% CO<sub>2</sub>. Stock plates of 293 cells were 20 trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LM(tk-) cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/mL penicillin/100 µg/mL streptomycin) at 37 °C, 5% CO<sub>2</sub>. Stock 25 plates of LM(tk-) cells were trypsinized and split 1:10 every 3-4 days.

LM(tk-) cells stably transfected with the human Y5 30 receptor were routinely converted from an adherent monolayer to a viable suspension. Adherent cells were harvested with trypsin at the point of confluence, resuspended in a minimal volume of complete DMEM for a cell count, and further diluted to a concentration of 10<sup>6</sup> cells/ml in suspension media (10% bovine calf serum, 10% 35 10X Medium 199 (Gibco), 9 mM NaHCO<sub>3</sub>, 25 mM glucose, 2 mM

L-glutamine, 100 units/ml penicillin/100 µg/ml streptomycin, and 0.05% methyl cellulose). The cell suspension was maintained in a shaking incubator at 37 °C, 5% CO<sub>2</sub> for 24 hours. Membranes harvested from cells grown in this manner may be stored as large, uniform batches in liquid nitrogen. Alternatively, cells may be returned to adherent cell culture in complete DMEM by distribution into 96-well microtiter plates coated with poly-D-lysine (0.01 mg/ml) followed by incubation at 37 °C, 5% CO<sub>2</sub> for 24 hours. Cells prepared in this manner yielded a robust and reliable NPY-dependent response in cAMP radio-immunoassays as further described hereinbelow.

Mouse embryonic fibroblast NIH-3T3 cells were grown on 150 mm plates in Dulbecco's Modified Eagle Medium (DMEM) with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37 °C, 5% CO<sub>2</sub>. Stock plates of NIH-3T3 cells were trypsinized and split 1:15 every 3-4 days.

Sf9 and Sf21 cells were grown in monolayers on 150 mm tissue culture dishes in TMN-FH media supplemented with 10% fetal calf serum, at 27°C, no CO<sub>2</sub>. High Five insect cells were grown on 150 mm tissue culture dishes in Ex-Cell 400™ medium supplemented with L-Glutamine, also at 27°C, no CO<sub>2</sub>.

#### Transient Transfection

All receptor subtypes studied (human and rat Y1, human and rat Y2, human and rat Y4, human and rat Y5) were transiently transfected into COS-7 cells by the DEAE-dextran method, using 1 µg of DNA /10<sup>6</sup> cells (Cullen, 1987). The human Y1 receptor was prepared using known methods (Larhammar, et al., 1992).

Stable Transfection

Human Y1, human Y2, and rat Y5 receptors were co-transfected with a G-418 resistant gene into the human embryonic kidney 293 cell line by a calcium phosphate  
5 transfection method (Cullen, 1987). Stably transfected cells were selected with G-418. Human Y4 and human Y5 receptors were similarly transfected into mouse fibroblast LM(tk-) cells and NIH-3T3 cells.

10 Binding of the compounds of the present invention to the human Y1, Y2, Y4 and Y5 receptors was evaluated using stably transfected 293 or LM(tk-) cells as described above. Stably transfected cell lines which may be used for binding assays include, for example, for the human Y1  
15 receptor, 293-hY1-5 (deposited June 4, 1996, under ATCC Accession No. CRL-12121), for the human Y2 receptor, 293-hY2-10 (deposited January 27, 1994, under ATCC Accession No. CRL-11537), for the human Y4 receptor, L-hY4-3 (deposited January 11, 1995, under ATCC Accession No. CRL-  
20 11779), and for the human Y5 receptor, L-hY5-7 (deposited November 15, 1995, under ATCC Accession No. CRL-11995).

Expression of other G-protein coupled receptors

25  $\alpha_1$  Human Adrenergic Receptors: To determine the binding of compounds to human  $\alpha_1$  receptors, LM(tk-) cell lines stably transfected with the genes encoding the  $\alpha_{1a}$ ,  $\alpha_{1b}$ , and  $\alpha_{1d}$  receptors were used. The nomenclature describing the  $\alpha_1$  receptors was changed recently, such that the  
30 receptor formerly designated  $\alpha_{1a}$  is now designated  $\alpha_{1d}$ , and the receptor formerly designated  $\alpha_{1c}$  is now designated  $\alpha_{1a}$  (ref). The cell lines expressing these receptors were deposited with the ATCC before the nomenclature change and reflect the subtype designations formerly assigned to  
35 these receptors. Thus, the cell line expressing the

receptor described herein as the  $\alpha_{1a}$  receptor was deposited with the ATCC on September 25, 1992, under ATCC Accession No. CRL 11140 with the designation L- $\alpha_{1c}$ . The cell line expressing receptor described herein as the  $\alpha_{1d}$  receptor was deposited with the ATCC on September 25, 1992, under ATCC Accession No. CRL 11138 with the designation L- $\alpha_{1A}$ . The cell line expressing the  $\alpha_{1b}$  receptor is designated L- $\alpha_{1B}$ , and was deposited on September 25, 1992, under ATCC Accession No. CRL 11139.

**$\alpha_2$  Human Adrenergic Receptors:** To determine the binding of compounds to human  $\alpha_2$  receptors, LM(tk-) cell lines stably transfected with the genes encoding the  $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$  receptors were used. The cell line expressing the  $\alpha_{2A}$  receptor is designated L- $\alpha_{2A}$ , and was deposited on November 6, 1992, under ATCC Accession No. CRL 11180. The cell line expressing the  $\alpha_{2B}$  receptor is designated L-NGC- $\alpha_{2B}$ , and was deposited on October 25, 1989, under ATCC Accession No. CRL 10275. The cell line expressing the  $\alpha_{2C}$  receptor is designated L- $\alpha_{2C}$ , and was deposited on November 6, 1992, under ATCC Accession No. CRL-11181. Cell lysates were prepared as described below (see Radioligand Binding to Membrane Suspensions), and suspended in 25mM glycylglycine buffer (pH 7.6 at room temperature). Equilibrium competition binding assay were performed using [ $^3$ H]rauwolscine (0.5nM), and nonspecific binding was determined by incubation with 10 $\mu$ M phentolamine. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

**Human Histamine  $H_1$  Receptor:** The coding sequence of the human histamine  $H_1$  receptor, homologous to the bovine  $H_1$  receptor, was obtained from a human hippocampal cDNA library, and was cloned into the eukaryotic expression vector pCEXV-3. The plasmid DNA for the  $H_1$  receptor is

designated pcEXV-H1, and was deposited on November 6, 1992, under ATCC Accession No. 75346. This construct was transfected into COS-7 cells by the DEAE-dextran method. Cells were harvested after 72 hours and lysed by sonication in 5mM Tris-HCl, 5mM EDTA, pH 7.5. The cell lysates were centrifuged at 1000 rpm for 5 min at 4°C, and the supernatant was centrifuged at 30,000 x g for 20 min. at 4°C. The pellet was suspended in 37.8 mM NaHPO<sub>4</sub>, 12.2 mM KH<sub>2</sub>PO<sub>4</sub>, pH 7.5. The binding of the histamine H<sub>1</sub> antagonist [<sup>3</sup>H]mepyramine (1nM, specific activity: 24.8 Ci/mM) was done in a final volume of 0.25 mL and incubated at room temperature for 60 min. Nonspecific binding was determined in the presence of 10 μM mepyramine. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

**Human Histamine H<sub>2</sub> Receptor:** The coding sequence of the human H<sub>2</sub> receptor was obtained from a human placenta genomic library, and cloned into the cloning site of PCEXV-3 eukaryotic expression vector. The plasmid DNA for the H<sub>2</sub> receptor is designated pcEXV-H2, and was deposited on November 6, 1992 under ATCC Accession No. 75345. This construct was transfected into COS-7 cells by the DEAE-dextran method. Cells were harvested after 72 hours and lysed by sonication in 5mM Tris-HCl, 5mM EDTA, pH 7.5. The cell lysates were centrifuged at 1000 rpm for 5 min at 4°C, and the supernatant was centrifuged at 30,000 x g for 20 min at 4 °C. The pellet was suspended in 37.8 mM NaHPO<sub>4</sub>, 12.2 mM K<sub>2</sub>PO<sub>4</sub>, pH 7.5. The binding of the histamine H<sub>2</sub> antagonist [<sup>3</sup>H]tiotidine (5nM, specific activity: 70 Ci/mM) was done in a final volume of 0.25 ml and incubated at room temperature for 60 min. Nonspecific binding was determined in the presence of 10 μM histamine. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

**Human Serotonin Receptors:**

5HT<sub>1Dα</sub>, 5HT<sub>1Dβ</sub>, 5HT<sub>1E</sub>, 5HT<sub>1F</sub> Receptors: LM(tk-) clonal cell lines stably transfected with the genes encoding each of these 5HT receptor subtypes were prepared as described above. The cell line for the 5HT<sub>1Dα</sub> receptor, designated as Ltk-8-30-84, was deposited on April 17, 1990, and accorded ATCC Accession No. CRL 10421. The cell for the 5HT<sub>1Dβ</sub> receptor, designated as Ltk-11, was deposited on April 17, 1990, and accorded ATCC Accession No. CRL 10422. The cell line for the 5HT<sub>1E</sub> receptor, designated 5 HT<sub>1E</sub>-7, was deposited on November 6, 1991, and accorded ATCC Accession No. CRL 10913. The cell line for the 5HT<sub>1F</sub> receptor, designated L-5-HT<sub>1F</sub>, was deposited on December 27, 1991, and accorded ATCC Accession No. ATCC 10957. Membrane preparations comprising these receptors were prepared as described below, and suspended in 50mM Tris-HCl buffer (pH 7.4 at 37°C) containing 10 mM MgCl<sub>2</sub>, 0.2 mM EDTA, 10μM pargyline, and 0.1% ascorbate. The binding of compounds was determined in competition binding assays by incubation for 30 minutes at 37°C in the presence of 5nM [<sup>3</sup>H]serotonin. Nonspecific binding was determined in the presence of 10μM serotonin. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

**Human 5HT<sub>2</sub> Receptor:** The coding sequence of the human 5HT<sub>2</sub> receptor was obtained from a human brain cortex cDNA library, and cloned into the cloning site of pCEXV-3 eukaryotic expression vector. This construct was transfected into COS-7 cells by the DEAE-dextran method. Cells were harvested after 72 hours and lysed by sonication in 5mM Tris-HCl, 5mM EDTA, pH 7.5. This cell line was deposited with the ATCC on October 31, 1989, designated as L-NGC-5HT<sub>2</sub>, and was accorded ATCC Accession No. CRL 10287. The cell lysates were centrifuged at 1000

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rpm for 5 minutes at 4°C, and the supernatant was centrifuged at 30,000 x g for 20 minutes at 4°C. The pellet was suspended in 50mM Tris-HCl buffer (pH 7.7 at room temperature) containing 10 mM MgSO<sub>4</sub>, 0.5mM EDTA, and 0.1% ascorbate. The potency of alpha-1 antagonists at 5HT<sub>2</sub> receptors was determined in equilibrium competition binding assays using [3H]ketanserin (1nM). Nonspecific binding was defined by the addition of 10μM mianserin. The bound radioligand was separated by filtration through GF/B filters using a cell harvester.

**Human 5-HT<sub>2</sub> Receptor:** A LM(tk-) clonal cell line stably transfected with the gene encoding the 5HT<sub>2</sub> receptor subtype was prepared as described above. The cell line for the 5HT<sub>2</sub> receptor, designated as L-5HT<sub>2AB</sub>, was deposited on October 20, 1992, and accorded ATCC Accession No. CRL 11166.

**Human Dopamine D<sub>3</sub> Receptor:** The binding of compounds to the human D<sub>3</sub> receptor was determined using membrane preparations from COS-7 cells transfected with the gene encoding the human D<sub>3</sub> receptor. The human dopamine D<sub>3</sub> receptor was prepared according to known methods (Sokoloff, P. et al. Nature, 347, 146, 1990, deposited with the EMBL Genbank as X53944). Cells were harvested after 72 hours and lysed by sonication in 5mM Tris-HCl, 5mM EDTA, pH 7.5. The cell lysates were centrifuged at 1000 rpm for 5 minutes at 4°C, and the supernatant was centrifuged at 30,000 x g for 20 minutes at 4°C. The pellet was suspended in 50 mM Tris-HCl (pH 7.4) containing 1mM EDTA, 5mM KCl, 1.5mM CaCl<sub>2</sub>, 4mM MgCl<sub>2</sub>, and 0.1% ascorbic acid. The cell lysates were incubated with [<sup>3</sup>H]spiperone (2nM), using 10μM (+)Butaclamol to determine nonspecific binding.

Membrane Harvest

Membranes were harvested from COS-7 cells 48 hours after transient transfection. Adherent cells were washed twice in ice-cold phosphate buffered saline (138 mM NaCl, 8.1 mM Na<sub>2</sub>HPO<sub>4</sub>, 2.5 mM KCl, 1.2 mM KH<sub>2</sub>PO<sub>4</sub>, 0.9 mM CaCl<sub>2</sub>, 0.5 mM MgCl<sub>2</sub>, pH 7.4) and lysed by sonication in ice-cold sonication buffer (20 mM Tris-HCl, 5 mM EDTA, pH 7.7). Large particles and debris were cleared by low speed centrifugation (200 x g, 5 min, 4 °C). Membranes were collected from the supernatant fraction by centrifugation (32,000 x g, 18 min, 4 °C), washed with ice-cold hypotonic buffer, and collected again by centrifugation (32,000 x g, 18 min, 4 °C). The final membrane pellet was resuspended by sonication into a small volume of ice-cold binding buffer (~1 ml for every 5 plates: 10 mM NaCl, 20 mM HEPES, 0.22 mM KH<sub>2</sub>PO<sub>4</sub>, 1.26 mM CaCl<sub>2</sub>, 0.81 mM MgSO<sub>4</sub>, pH 7.4). Protein concentration was measured by the Bradford method (Bradford, 1976) using Bio-Rad Reagent, with bovine serum albumin as a standard. Membranes were held on ice for up to one hour and used fresh, or flash-frozen and stored in liquid nitrogen.

Membranes were prepared similarly from 293, LM(tk-), and NIH-3T3 cells. To prepare membranes from baculovirus infected cells, 2 x 10<sup>7</sup> Sf21 cells were grown in 150mm tissue culture dishes and infected with a high-titer stock of hY5BB3. Cells were incubated for 2-4 days at 27°C, no CO<sub>2</sub>, before harvesting and membrane preparation as described above.

Membranes were prepared similarly from dissected rat hypothalamus. Frozen hypothalami were homogenized for 20 seconds in ice-cold sonication buffer with the narrow probe of a Virtishear homogenizer at 1000 rpm (Virtis, Gardiner, NY). Large particles and debris were cleared by



centrifugation (200 x g, 5 min, 4 °C) and the supernatant fraction was reserved on ice. Membranes were further extracted from the pellet by repeating the homogenization and centrifugation procedure two more times. The supernatant fractions were pooled and subjected to high speed centrifugation (100,000 x g, 20 min. 4 °C). The final membrane pellet was resuspended by gentle homogenization into a small volume of ice-cold binding buffer (1 mL/ gram wet weight tissue) and held on ice for up to one hour, or flash-frozen and stored in liquid nitrogen.

#### Radioligand Binding to Membrane Suspensions

Membrane suspensions were diluted in binding buffer supplemented with 0.1% bovine serum albumin to yield an optimal membrane protein concentration so that  $^{125}\text{I}$ -PYY (or alternative radioligand such as  $^{125}\text{I}$ -NPY,  $^{125}\text{I}$ -PYY<sub>3-36</sub>, or  $^{125}\text{I}$ -[Leu<sup>31</sup>Pro<sup>34</sup>]PYY) bound by membranes in the assay was less than 10% of  $^{125}\text{I}$ -PYY (or alternative radioligand) delivered to the sample (100,000 dpm/sample = 0.08 nM for competition binding assays).  $^{125}\text{I}$ -PYY (or alternative radioligand) and peptide competitors were also diluted to desired concentrations in supplemented binding buffer. Individual samples were then prepared in 96-well polypropylene microtiter plates by mixing  $^{125}\text{I}$ -PYY (25  $\mu\text{L}$ ) (or alternative radioligand), competing peptides or supplemented binding buffer (25  $\mu\text{L}$ ), and finally, membrane suspensions (200  $\mu\text{l}$ ). Samples were incubated in a 30 °C water bath with constant shaking for 120 min. Incubations were terminated by filtration over Whatman GF/C filters (pre-coated with 1% polyethyleneimine and air-dried before use), followed by washing with 5 mL of ice-cold binding buffer. Filter-trapped membranes were impregnated with MultiLex solid scintillant (Wallac, Turku, Finland) and counted for  $^{125}\text{I}$  in a Wallac Beta-

Plate Reader. Non-specific binding was defined by 300 nM human NPY for all receptors except the Y4 subtypes; 100 nM human PP was used for the human Y4 and 100 nM rat PP for the rat Y4. Specific binding in time course and competition studies was typically 80%; most non-specific binding was associated with the filter. Binding data were analyzed using nonlinear regression and statistical techniques available in the GraphPAD Prism package (San Diego, CA).

Functional Assay: Radioimmunoassay of cAMP

Stably transfected cells were seeded into 96-well microtiter plates and cultured until confluent. To reduce the potential for receptor desensitization, the serum component of the media was reduced to 1.5% for 4 to 16 hours before the assay. Cells were washed in Hank's buffered saline, or HBS (150 mM NaCl, 20 mM HEPES, 1 mM CaCl<sub>2</sub>, 5 mM KCl, 1 mM MgCl<sub>2</sub>, and 10 mM glucose) supplemented with 0.1% bovine serum albumin plus 5 mM theophylline and pre-equilibrated in the same solution for 20 min at 37 °C in 5% CO<sub>2</sub>. Cells were then incubated 5 min with 10 μM forskolin and various concentrations of receptor-selective ligands. The assay was terminated by the removal of HBS and acidification of the cells with 100 mM HCl. Intracellular cAMP was extracted and quantified with a modified version of a magnetic bead-based radioimmunoassay (Advanced Magnetix, Cambridge, MA). The final antigen/antibody complex was separated from free <sup>125</sup>I-cAMP by vacuum filtration through a PVDF filter in a microtiter plate (Millipore, Bedford, MA). Filters were punched and counted for <sup>125</sup>I in a Packard gamma counter. Binding data were analyzed using nonlinear regression and statistical techniques available in the GraphPAD Prism package (San Diego, CA).

Functional Assay: Intracellular calcium mobilization

The intracellular free calcium concentration was measured by microspectrofluorimetry using the fluorescent indicator dye Fura-2/AM (ref). Stably transfected cells were seeded onto a 35 mm culture dish containing a glass coverslip insert. Cells were washed with HBS and loaded with 100  $\mu$ l of Fura-2/AM (10  $\mu$ M) for 20 to 40 min. After washing with HBS to remove the Fura-2/AM solution, cells were equilibrated in HBS for 10 to 20 min. Cells were then visualized under the 40X objective of a Leitz Fluovert FS microscope and fluorescence emission was determined at 510 nm with excitation wave lengths alternating between 340 nm and 380 nm. Raw fluorescence data were converted to calcium concentrations using standard calcium concentration curves and software analysis techniques.

In vivo STUDIES IN RATSFood intake in satiated rats

For these determinations food intake maybe measured in normal satiated rats after intracerebroventricular application (i.c.v.) of NPY in the presence or absence of the test compound. Male Sprague Dawley rats ciba-Geigy AG, Sisseln, Switzerland weighing between 180g and 220 g are used for all experiments. The rats are individually housed in stainless steel cages and maintained on an 11:13 h light-dark cycle (lights off at 18:00 h) at a controlled temperature of 21-23 °C at all times. Water and food (NAFAG lab chow pellets, NAFAG, Gossau, Switzerland) are available ad libidum.

Rats under pentobarbital anesthesia are stereotaxically implanted with a stainless steel guide cannula targeted

at the right lateral ventricle. Stereotaxic coordinates, with the incisor bar set -2.0mm below interaural line, are: -0.8mm anterior and +1.3mm lateral to bregma. The guide cannula is placed on the dura. Injection cannulas extend the guide cannulas -3.8mm ventrally to the skull surface. Animals are allowed at least 4 days of recovery postoperatively before being used in the experiments. Cannula placement is checked postoperatively by testing all rats for their drinking response to a 50 ng intracerebroventricular (i.c.v.) injection of angiotensin II. Only rats which drink at least 2.5 ml of water within 30 min. after angiotensin II injection are used in the feeding studies.

All injections are made in the morning 2 hours after light onset. Peptides are injected in artificial cerebrospinal fluid (ACSF) in a volume of 5 $\mu$ l. ACSF contains: NaCl 124mM, KCl 3.75 mM, CaCl<sub>2</sub> 2.5 mM, MgSO<sub>4</sub> 2.0 mM, KH<sub>2</sub>PO<sub>4</sub> 0.22mM, NaHCO<sub>3</sub> 26 mM and glucose 10 mM. porcine-NPY is dissolved in artificial cerebrospinal fluid (ACS). For i.c.v. injection the test compounds are preferably dissolved in DMSO/water (10%, v/v). The vehicle used for intraperitoneal (i.p.), subcutaneous (s.c.) or oral (p.o.) delivery of compounds is preferably water, physiological saline or DMSO/water (10% v/v), or cremophor/water (20% v/v), respectively.

Animals which are treated with both test compounds and p-NPY are treated first with the test compound. Then, 10 min. after i.c.v. application of the test compound or vehicle (control), or 30-60 min after i.p., s.c. and p.o. application of the test compound or vehicle, 300 pmol of NPY is administered by intracerebroventricular (i.c.v.) application.

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Food intake may be measured by placing preweighed pellets into the cages at the time of NPY injection. Pellets are removed from the cage subsequently at each selected time point and replaced with a new set of preweighed pellets.

5 The food intake of animals treated with test compound may be calculated as a percentage of the food intake of control animals, i.e., animals treated with vehicle. Alternatively, food intake for a group of animals subjected to the same experimental condition may be

10 expressed as the mean  $\pm$  S.E.M. Statistical analysis is performed by analysis of variance using the Student-Newman-Keuls test.

#### Food intake in food-deprived rats

15 Food-deprivation experiments are conducted with male Sprague-Dawley rats weighing between 220 and 250 g. After receipt, the animals are individually housed for the duration of the study and allowed free access to normal food together with tap water. The animals are

20 maintained in a room with a 12 h light/dark cycle (8:00 a.m. to 8:00 p.m. light) at 24 °C and monitored humidity. After placement into individual cages the rats undergo a 4 day equilibration period, during which they are habituated to their new environment and to eating a

25 powdered or pellet diet (NAFAG, Gossau, Switzerland).

At the end of the equilibration period, food is removed from the animals for 24 hours starting at 8:00 a.m. At the end of the fasting period compound or vehicle may be

30 administered to the animals orally or by injection intraperitoneally or intravenously. After 10 - 60 min. food is returned to the animals and their food intake monitored at various time periods during the following 24 hour period. The food intake of animals treated with

35 test compound may be calculated as a percentage of the

food intake of control animals (i.e., animals treated with vehicle). Alternatively, food intake for a group of animals subjected to the same experimental conditions may be expressed as the mean  $\pm$  S.E.M.

5

#### Food intake in obese Zucker rats

The antiobesity efficacy of the compounds according to the present invention might also be manifested in Zucker obese rats, which are known in the as an animal model of obesity. These studies are conducted with male Zucker fatty rats (fa/fa Harlan CPB, Austerlitz NL) weighing between 480g and 500g. Animals are individually housed in metabolism cages for the duration of the study and allowed free access to normal powdered food and water. The animals are maintained in a room with a 12 h light/dark cycle (light from 8:00 A.M. to 8:00 P.M.) at 24°C and monitored humidity. After placement into the metabolism cages the rats undergo a 6 day equilibration period, during which they are habituated to their new environment and to eating a powdered diet. At the end of the equilibration period, food intake during the light and dark phases is determined. After a 3 day control period, the animals are treated with test compounds or vehicle (preferably water or physiological saline or DMSO/water (10%, v/v) or cremophor/water (20%, v/v)). Food intake is then monitored over the following 3 day period to determine the effect of administration of test compound or vehicle alone. As in the studies described hereinabove, food intake in the presence of drug may be expressed as a percentage of the food intake of animals treated with vehicle.

30

#### Materials

Cell culture media and supplements were from Specialty Media (Lavallette, NJ). Cell culture plates (150 mm and

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96-well microtiter) were from Corning (Corning, NY). Sf9, Sf21, and High Five insect cells, as well as the baculovirus transfer plasmid, pBlueBacIII™, were purchased from Invitrogen (San Diego, CA). TMN-FH insect medium complemented with 10% fetal calf serum, and the baculovirus DNA, BaculoGold™, was obtained from Pharmingen (San Diego, CA.). Ex-Cell 400™ medium with L-Glutamine was purchased from JRH Scientific. Polypropylene 96-well microtiter plates were from Co-star (Cambridge, MA). All radioligands were from New England Nuclear (Boston, MA). Commercially available NPY and related peptide analogs were either from Bachem California (Torrance, CA) or Peninsula (Belmont, CA); [D-Trp<sup>32</sup>]NPY and PP C-terminal fragments were synthesized by custom order from Chiron Mimotopes Peptide Systems (San Diego, CA). Bio-Rad Reagent was from Bio-Rad (Hercules, CA). Bovine serum albumin (ultra-fat free, A-7511) was from Sigma (St. Louis, MO). All other materials were reagent grade.

**EXPERIMENTAL RESULTS**

Applicants have synthesized and evaluated the binding and functional properties of several compounds at the cloned human Y1, human Y2, human Y4, and human Y5 receptors. As shown below in Table 5, applicants have discovered several compounds which not only bind selectively to the human Y5 receptor but also act as Y5 receptor antagonists, as measured by their ability to block NPY-induced inhibition of cAMP accumulation in forskolin-stimulated LM(tk-) cells stably transfected with the cloned human Y5 receptor.

**Table 5: Evaluation of human Y5 receptor antagonists**

The ability of the compounds to antagonize the Y-type receptors is reported as the  $K_b$ . The  $K_b$  is derived from the  $EC_{50}$ , or concentration of half-maximal effect, in the presence ( $EC_{50}$ ) or absence ( $EC_{50}'$ ) of compound, according to the equation:  $K_b = [NPY] / ((EC_{50}/EC_{50}') - 1)$ . Results shown are representative of at least three independent experiments.

N.D. = Not determined.

**Table 5**

	Binding Affinity (K <sub>i</sub> (nM) vs. <sup>125</sup> I-PYY)				
Example	Human Receptor				K <sub>b</sub> (nM)
-	Y1	Y2	Y4	Y5	-
31	5550	1000	8020	14	6.0
32	3550	955	11700	11	23



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	Binding Affinity (K <sub>i</sub> (nM) vs. <sup>125</sup> I-PYY)				
36	16000	7760	20400	8.3	26
38	13000	1610	18500	9.8	16
40	17200	7570	27500	11	3.0
37	14500	617	21500	26	38
77	3240	851	13100	17	311
44	23700	58200	19300	14	50
45	48700	5280	63100	28	49

10 Several of the compounds were further tested using in  
vivo animal models of feeding behavior. Since NPY is the  
strongest known stimulant of feeding behavior,  
experiments were performed with several compounds to  
15 evaluate the effect of the compounds described above on  
NPY-induced feeding behavior in satiated rats.

First, 300 pmole of porcine NPY in vehicle (A.C.S.F.) was  
administered by intracerebroventricular (i.c.v.)  
injection, along with i.p. administration of compound  
20 vehicle (10% DMSO/water), and the food intake of NPY-  
stimulated animals was compared to food intake in animals  
treated with the vehicles. The 300 pmole injection of  
NPY was found to significantly induce food intake ( $p <$   
0.05; Student-Newman-Keuls).

25 Using the 300 pmole dose of NPY found to be effective to  
stimulate feeding, other animals were treated with the  
compounds by intraperitoneal (i.p.) administration,

followed 30-60 minutes later by i.c.v. NPY administration, and measurement of subsequent food intake. As shown in Table 6, NPY-induced food intake was significantly reduced in animals first treated with the compounds ( $p < 0.05$ ; Student-Newman-Keuls). These experiments demonstrate that NPY-induced food intake is significantly reduced by administration to animals of a compound which is a Y5-selective antagonist.

Table 6. NPY-induced cumulative food intake in rats treated with either the i.c.v. and i.p. vehicles (control), 300 pmole NPY alone (NPY), or in rats treated first with compound and then NPY (NPY + compound). Food intake was measured 4 hours after stimulation with NPY. Food intake is reported as the mean  $\pm$  S.E.M. intake for a group of animals.

Table 6

Example	31	32
Compound Dose (mg/kg i.p.)	10	30
control (vehicles only)	2.4 $\pm$ 0.7	2.9 $\pm$ 0.8
NPY	5.8 $\pm$ 0.5	4.9 $\pm$ 0.4
NPY + compound	3.8 $\pm$ 0.4	1.5 $\pm$ 0.6

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Since food deprivation induces an increase in the hypothalamic NPY levels, it has been postulated that food intake following a period of food deprivation is NPY-mediated. Therefore, the Y5 antagonists of Table 5 were administered to conscious rats following a 24h food deprivation. Each of the human Y5 receptor antagonists shown in Table 5 was able to significantly reduce NPY-induced food intake in the animals, as shown below in Table 7. The food intake of animals treated with test compound is reported as a percentage of the food intake measured for control animals (treated with vehicle), i.e., 25% means the animals treated with the compound consumed only 25% as much food as the control animals. Measurements were performed two hours after administration of the test compound.

**Table 7 Two-hour food intake of NPY-stimulated rats.**  
Food intake is expressed as the percentage of intake compared to control rats.

5

Example	Mean (%)
31	27
32	36
36	35
38	80
40	55
37	58
77	32
44	73
45	84

10

15

20

These experiments indicate that the compounds of the present invention inhibit food intake in rats, especially when administered in a range of about 0.01 to about 100 mg/kg rat, by either oral, intraperitoneal or intravenous administration. The animals appeared normal during these experiments, and no ill effects on the animals were observed after the termination of the feeding experiments.

25

The binding properties of the compounds were also evaluated with respect to other cloned human G-protein coupled receptors. As shown in Table 8, below, the Y5-

selective compounds described hereinabove exhibited lower affinity for receptors other than the Y-type receptors.

Table 8 Cross-reactivity of compounds at other cloned human receptors

[illegible]

Table 8 (continued)

[illegible]

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EXPERIMENTAL DISCUSSION

Y5 receptors are highly attractive targets for appetite and weight control based on several lines of research (Sahu and Kalra, 1993). NPY is the most potent stimulant of feeding behavior yet described (Clark et al., 1984; Levine and Morley, 1984; Stanley and Leibowitz, 1984). Direct injection of NPY into the hypothalamus of rats can increase food intake ~ 10-fold over a 4-hour period (Stanley et al., 1992). NPY-stimulated rats display a preference for carbohydrates over protein and fat (Stanley et al., 1985). Interestingly, NPY and NPY mRNA are increased in food-deprived rats (Brady et al., 1990; O' Shea and Gundlach, 1991) and also in rats which are genetically obese (Sanacora et al., 1990) or made diabetic by treatment with streptozotocin (White et al., 1990). One potential explanation is that NPY, a potent stimulant of feeding behavior in normal rats, is disregulated in the overweight or diabetic animal so that food intake is increased, accompanied by obesity. The physiological stress of obesity increases the risk for health problems such as cardiovascular malfunction, osteoarthritis, and hyperinsulinemia, together with a worsened prognosis for adult-onset diabetes. A nonpeptide antagonist targeted to the Y5 receptor could therefore be effective as a way to control not only appetite and body weight but an entire range of obesity- and diabetes-related disorders (Dryden et al., 1994). There is also neurochemical evidence to suggest that NPY-mediated functions are disregulated in eating disorders such as bulimia and anorexia nervosa, so that they too could be responsive to treatment by a Y5-selective drug. It has been proposed, for example, that food intake in NPY-stimulated rats mimics the massive food consumption associated with binge eating in bulimia (Stanley, 1993).

CSF levels of PYY but not NPY were elevated in bulimic patients who abstained from bingeing, and then diminished when bingeing was allowed (Berrettini et al., 1988). Conversely, NPY levels were elevated in underweight anorectic patients and then diminished as body weight was normalized (Kaye et al., 1990).

As described above, the human and rat *in vitro* expression models were used in combination to screen for compounds intended to modulate NPY-dependent feeding behavior. Using this approach, applicants have discovered several compounds which inhibit feeding behavior in animal models, which should lead to additional drug discoveries. The compounds according to the present invention inhibit food intake in Zucker obese rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal or intravenous administration.

The Y5 pharmacological profile further offers a new standard by which to review the molecular basis of all NPY-dependent processes. Such an exercise suggests that the Y5 receptor is likely to have a physiological significance beyond feeding behavior. It has been reported, for example, that a Y-type receptor can regulate luteinizing hormone releasing hormone (LHRH) release from the median eminence of steroid-primed rats *in vitro* with an atypical Y1 pharmacological profile. NPY, NPY<sub>2-36</sub>, and LP-NPY were all effective at 1 $\mu$ M but deletion of as few as four amino acids from the N-terminus of NPY destroyed biological activity. The Y5 may therefore represent a therapeutic target for sexual or reproductive disorders. It is worth while considering that the Y5 is so similar in pharmacological profile to the other Y-type receptors that it may have been



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overlooked among a mixed population of Y1, Y2 and Y4 receptors. Certain functions now associated with these subtypes could therefore be reassigned to Y5 as our pharmacological tools grow more sophisticated. By  
5 offering new insight into NPY receptor pharmacology, the Y5 thereby provides a greater clarity and focus in the field of drug design.

**TABLE 9: Pathophysiological Conditions Associated With NPY**

5	The following pathological conditions have been linked to either 1) application of exogenous NPY, or 2) changes in levels of endogenous NPY.		
10	1	obesity	Sahu and Kalra, 1993
	2	eating disorders (anorexia and bulimia nervosa)	Stanley, 1993
	3	sexual/reproductive function	Clark, 1994
	4	depression	Heilig and Weiderlov, 1990
	5	anxiety	Wahlestedt et al., 1993
	6	cocaine addiction	Wahlestedt et al., 1991
	7	gastric ulcer	Penner et al., 1993
15	8	memory loss	Morley and Flood, 1990
	9	pain	Hua et al., 1991
	10	epileptic seizure	Rizzi et al., 1993
	11	hypertension	Zukowska-Grojec et al., 1993
	12	subarachnoid hemorrhage	Abel et al., 1988
20	13	shock	Hauser et al., 1993
	14	circadian rhythm	Albers and Ferris, 1984
	15	nasal congestion	Lacroix et al., 1988
	16	diarrhea	Cox and Cuthbert, 1990
25	17	neurogenic voiding dysfunction	Zoubek et al., 1993

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A successful strategy for the design of a Y5-receptor based drug or for any drug targeted to single G protein-coupled receptor subtype involves the screening of candidate compounds 1) in radioligand binding assays so as to detect affinity for cross-reactive G protein-coupled receptors, and 2) in physiological assays so as to detect undesirable side effects. In the specific process of screening for a Y5-selective drug, the receptor subtypes most likely to cross-react and therefore most important for radioligand binding screens include the other "Y-type" receptors, Y1, Y2, Y3, and Y4. Cross-reactivity between the Y5 and any of the other subtypes could result in potential complications as suggested by the pathophysiological indications listed in Table 9. In designing a Y5 antagonist for obesity and appetite control, for example, it is important not to design a Y1 antagonist resulting in hypertension or increased anxiety, a Y2 antagonist resulting in memory loss, or a Y4 antagonist resulting in increased appetite.

TABLE 10: Y-Type Receptor Indications

	Y-type Receptor Indications	Receptor Subtype	Drug Activity	Reference
5	obesity, appetite disorder	atypical Y1	antagonist	Sahu and Kalra, 1993
10	adult onset diabetes	atypical Y1	antagonist	Sahu and Kalra, 1993
	bulimia nervosa	atypical Y1	antagonist	Stanley, 1993
15	pheochromoc ytoma- induced hypertensio n	Y1	antagonist	Grouzman et al., 1989
20	subarachnoi d hemorrhage	Y1	antagonist	Abel et al., 1988
	neurogenic vascular hypertrophy	Y1 Y2	antagonist antagonist	Zukowska- Grojec et al., 1993
25	epileptic seizure	Y2	antagonist	Rizzi et al., 1993
30	hypertensio n: central, peripheral regulation	peripheral Y1 central Y3 central Y2	antagonist agonist antagonist	Grundemar and Hakanson, 1993 Barraco et al., 1991
	obesity, appetite disorder	Y4 or PP	agonist	Malaisse- Lagae et al., 1977
35	anorexia nervosa	atypical Y1	agonist	Berrettin i et al., 1988

	anxiety	Y1	agonist	Wahlestedt et al., 1993
	cocaine addiction	Y1	agonist	Wahlestedt et al., 1991
5	stress-induced gastric ulcer	Y1 Y4 or PP	agonist agonist	Penner et al., 1993
	memory loss	Y2	agonist	Morley and Flood, 1990
	pain	Y2	agonist	Hua et al., 1991
10	shock	Y1	agonist	Hauser et al., 1993
	sleep disturbance s, jet lag	Y2	not clear	Albers and Ferris, 1984
15	nasal decongestion	Y1 Y2	agonist agonist	Lacroix et al., 1988
	diarrhea	Y2	agonist	Cox and Cuthbert, 1990

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The Y5 receptor represents an enormous opportunity for the development of novel and selective drug therapies, particularly those targeted to appetite and weight control, but also for memory loss, depression, anxiety, gastric ulcer, epileptic seizure, pain, hypertension, subarachnoid hemorrhage, sleeping disturbances, nasal congestion, neurogenic voiding dysfunction, and diarrhea.

In particular, the discovery of Y5-selective antagonists which inhibit food intake in rats provides a method of modifying feeding behavior in a wide variety of vertebrate animals.

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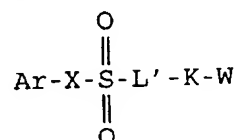
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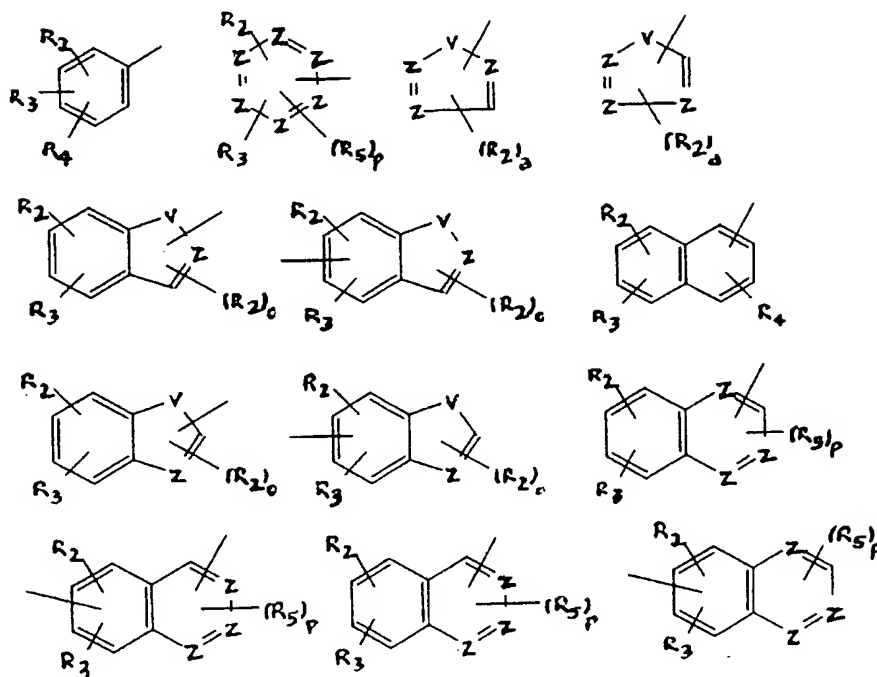
What is claimed is:

1. A compound having the structure:

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wherein Ar is



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wherein each Z is independently N or C;

wherein each Y is independently N or C;

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wherein p is an integer from 0 to 2;

wherein o is an integer from 0 to 1 and a is an integer from 0 to 3;

wherein V is S, O, N, or NR<sub>5</sub>;

wherein X is a single bond or -NH-;

5 wherein each R<sub>2</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>4</sub> alkenyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>; 10 phenoxy; phenyl; pyridyl; thiophenyl; naphthyl; phthalimide; C<sub>5</sub>-C<sub>7</sub> lactam, C<sub>5</sub>-C<sub>7</sub> cyclic imide, C<sub>5</sub>-C<sub>7</sub> cyclic amino; wherein the phthalimide, lactam, cyclic imide, or cyclic amine is linked by nitrogen; and wherein the phenoxy, phenyl, pyridyl, 15 thiophenyl, naphthyl, phthalimide, lactam, cyclic imide, or cyclic amine is substituted with H, F, Cl, Br, I, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio, or NO<sub>2</sub>;

20 wherein each R<sub>3</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>4</sub> alkenyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>; 25 or R<sub>2</sub> and R<sub>3</sub> present on adjacent carbon atoms can constitute C<sub>5</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> heterocycloalkyl or C<sub>5</sub>-C<sub>7</sub> heteroaryl;

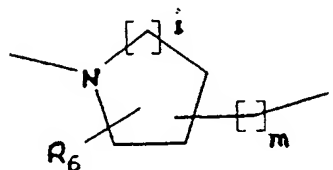
30 wherein each R<sub>4</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; or SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>; 35

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wherein each  $R_5$  is independently H;  $C_1-C_3$  alkyl;  $C_1-C_3$  monohaloalkyl; or  $C_1-C_3$  polyhaloalkyl;

wherein  $L'$  is  $-NR_1-L-$  or

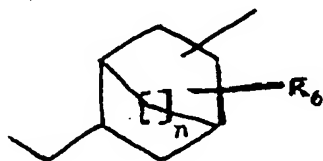
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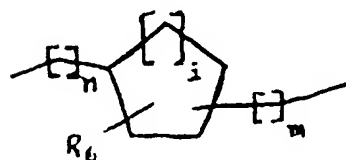
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wherein  $L$  is  $C_3-C_9$  alkyl;  $C_3-C_9$  alkenyl;  $C_3-C_9$  alkynyl;

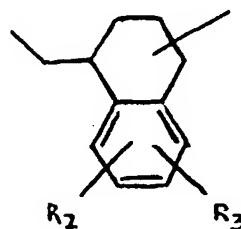
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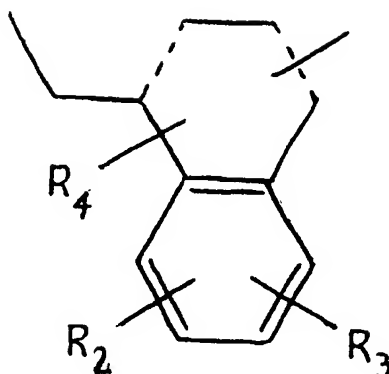


30

or

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wherein  $R_1$  is H; or  $C_1$ - $C_3$  straight chained alkyl;

wherein the alkyl, alkenyl or alkynyl is substituted with H,  $OR_5$ , CN,  $C_1$ - $C_6$  alkyl,  $CH_2OR_5$ ,  $CON(R_5)_2$ ,  $CO_2R_5$ , phenyl, pyridyl, thiophenyl or naphthyl;

20

wherein one dashed line is a double bond and the other dashed line is a single bond;

25

wherein each  $R_6$  is independently H; CN;  $OR_5$ ;  $C_1$ - $C_5$  alkyl;  $CH_2OR_5$ ;  $CON(R_5)_2$ ;  $CO_2R_5$ ; phenyl; pyridyl; thiophenyl or naphthyl; wherein the phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio, or  $NO_2$ ;

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wherein  $i$  is an integer from 1 to 4; wherein  $n$  is an integer from 0 to 3; wherein  $m$  is an integer from 0 to 3;

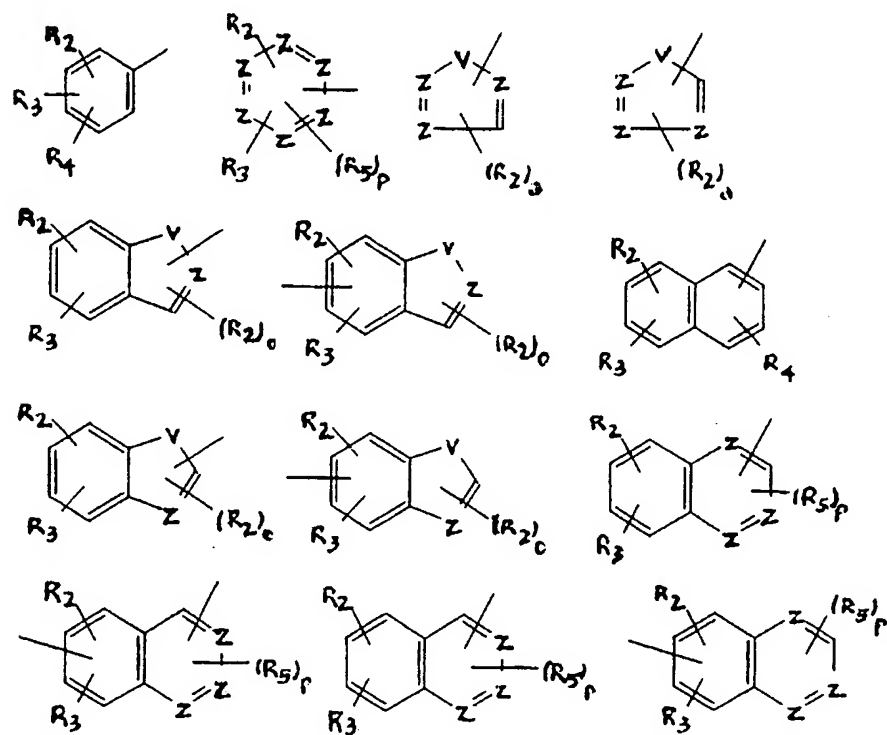
-135-

5 wherein K is  $-\text{CH}_2-\text{NR}_{10}-\text{CHR}_7-(\text{CH}_2)_j-$ ;  $-\text{CH}_2-\text{NR}_{10}-\text{CO}-(\text{CH}_2)_j-$   
;  $-\text{CH}_2-\text{NH}-\text{CO}-\text{NH}-(\text{CH}_2)_j-$ ;  $-\text{CO}-\text{NH}-\text{CHR}_7-(\text{CH}_2)_j-$ ;  $-\text{CH}_2-\text{NR}_{10}-$   
 $\text{CO}-\text{CHR}_7-(\text{CH}_2)_j$ ;  $-\text{CH}_2-\text{NR}_{10}-\text{CS}-(\text{CH}_2)_j-$ ;  $-\text{CH}_2-\text{NH}-\text{CS}-\text{NH}-$   
 $(\text{CH}_2)_j-$ ;  $-\text{CS}-\text{NH}-\text{CHR}_7-(\text{CH}_2)_j-$ ;  $-\text{CH}_2-\text{NR}_{10}-\text{CS}-\text{CHR}_7-(\text{CH}_2)_j$ ;  
or  $-\text{CH}_2-\text{N}=\text{CSR}_1-\text{NH}-(\text{CH}_2)_j$ ;

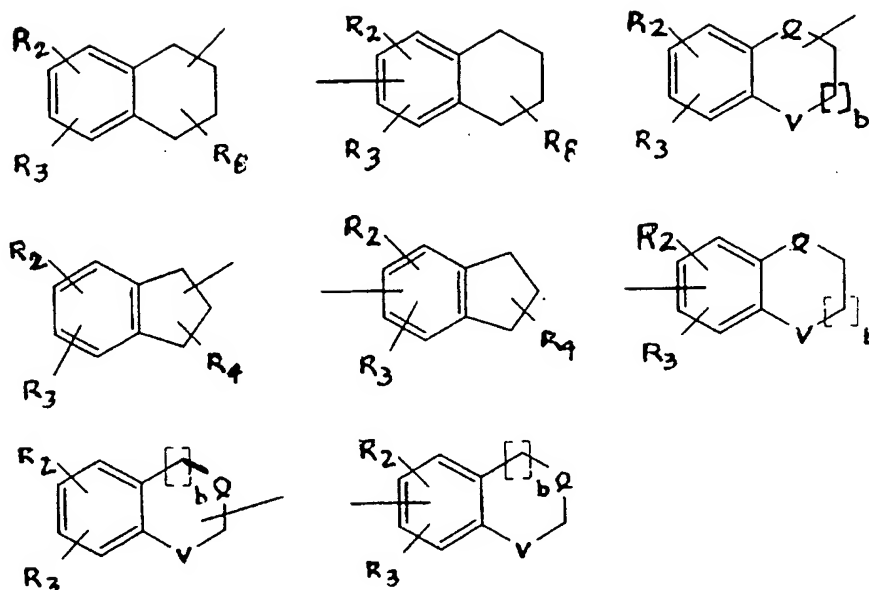
wherein j is an integer from 0 to 3;

10 wherein  $R_7$  is H;  $\text{C}_1-\text{C}_6$  alkyl;  $\text{CH}_2\text{OR}_5$ ;  $(\text{CH}_2)_p\text{NHCO}_2\text{R}_5$ ;  
 $(\text{CH}_2)_p\text{NHSO}_2\text{R}_5$ ;  $\text{CH}_2\text{N}(\text{R}_{11})_2$ ; phenyl; pyridyl; thiophenyl;  
or naphthyl;

wherein W is







wherein Q is O; S; N; NR<sub>9</sub>; or C(R<sub>5</sub>)<sub>2</sub>;

5

wherein b is an integer from 1 to 2;

10

wherein R<sub>8</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; =O; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; or SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;

15

wherein R<sub>9</sub> is H; C<sub>1</sub>-C<sub>3</sub> alkyl; COR<sub>5</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>;

wherein R<sub>10</sub> is H; or C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein R<sub>11</sub> is H; COR<sub>5</sub>; COR<sub>12</sub>; SO<sub>2</sub>R<sub>5</sub>; SO<sub>2</sub>R<sub>12</sub>; and

wherein  $R_{12}$  is phenoxy; phenyl, pyridyl; thiophenyl; or naphthyl; wherein the phenoxy, phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkylthio,  $NO_2$ , phenyl, pyridyl or thiophenyl;

or a pharmaceutically acceptable salt thereof.

2. An (+) enantiomer of the compound of claim 1.

3. An (-) enantiomer of the compound of claim 1.

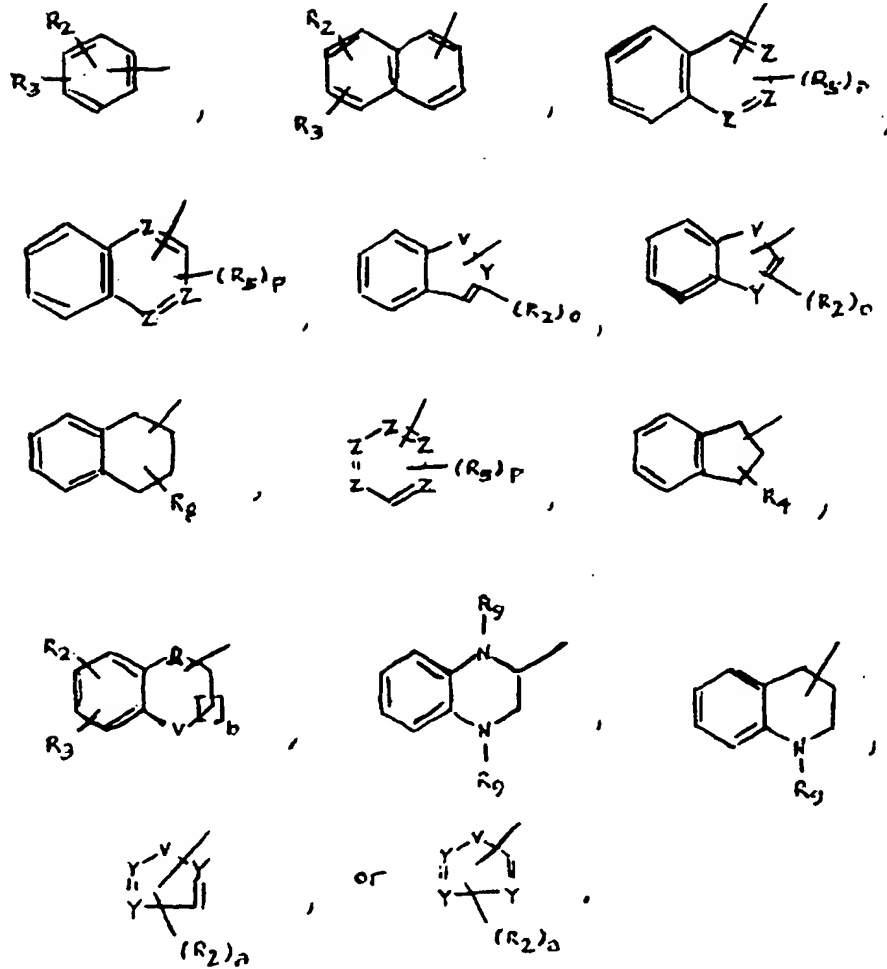
4. A compound of claim 1, wherein  $R_1$  is H;

wherein L is selected from  $C_3-C_9$  alkyl or

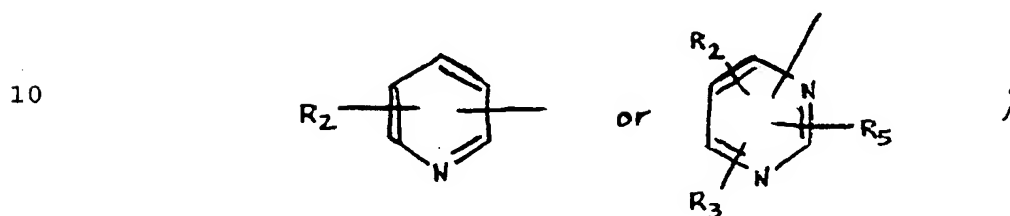
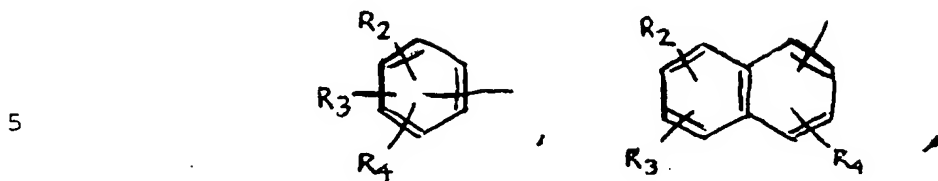


wherein the alkyl is substituted with H,  $OR_5$ , CN,  $C_1-C_6$  alkyl,  $CH_2OR_5$ ,  $CON(R_5)_2$ ,  $CO_2R_5$ , phenyl, pyridyl, thiophenyl or naphthyl; and

wherein W is



5. A compound of claim 4, wherein Ar is selected from:

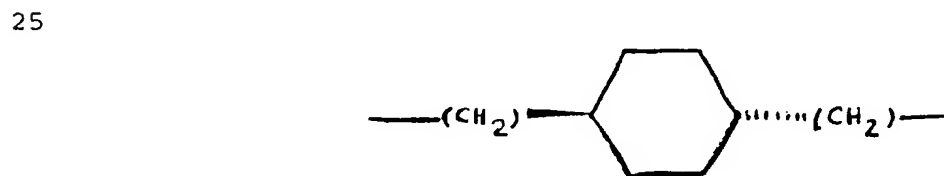


15 wherein each of R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> is independently H; F, Cl, Br or I; NO<sub>2</sub>; OH; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; or N(R<sub>5</sub>)<sub>2</sub>;

20 wherein X is a single bond;

wherein each R<sub>5</sub> is independently C<sub>1</sub>-C<sub>4</sub> alkyl;

wherein L is selected from C<sub>5</sub>-alkyl or C<sub>7</sub>-alkyl;

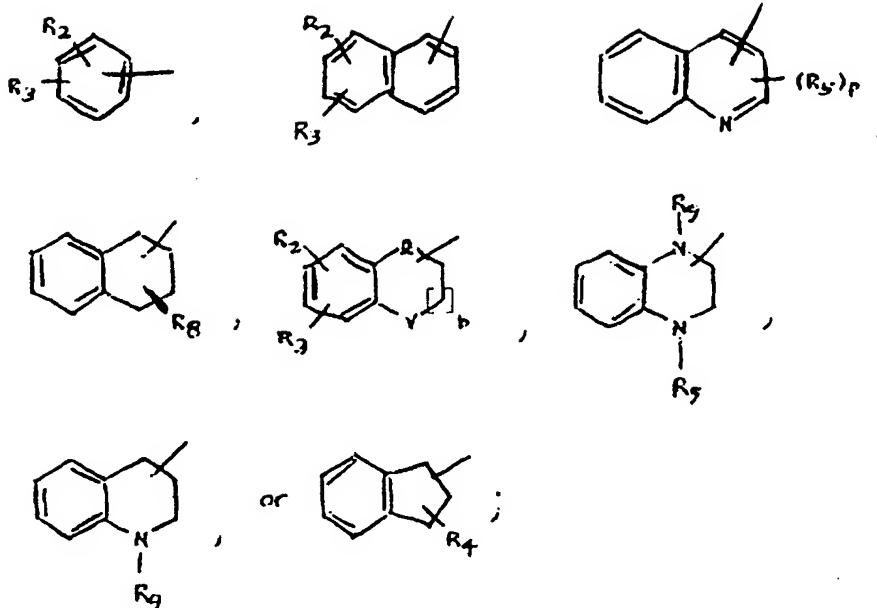


or

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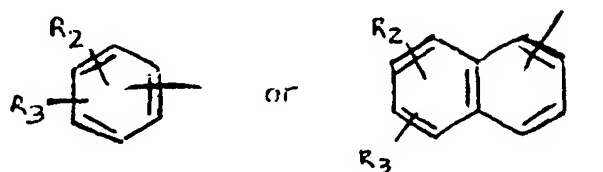
35 wherein R<sub>7</sub> is H; CH<sub>2</sub>OH; or CH<sub>2</sub>OR<sub>5</sub>;

wherein W is



and wherein  $R_7$  is H; or  $C_1$ - $C_3$  alkyl.

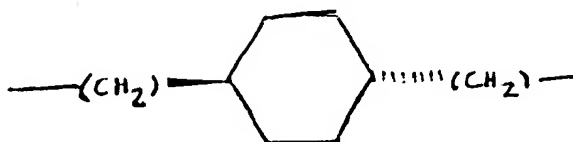
- 5 6. A compound of claim 5, wherein Ar is selected from:



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7. A compound of claim 6, wherein L is

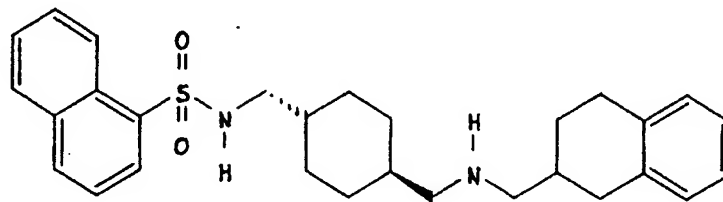
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8. A compound of claim 7, wherein K is  
-CH<sub>2</sub>-NR<sub>10</sub>-CHR<sub>7</sub>-(CH<sub>2</sub>)<sub>3</sub>-.
9. The compound of claim 8, wherein the compound is  
selected from the group consisting of:

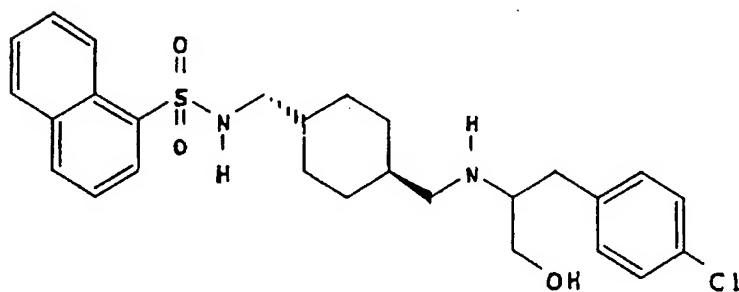
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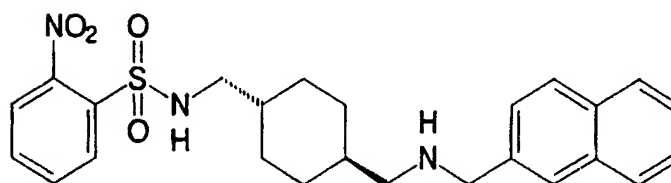
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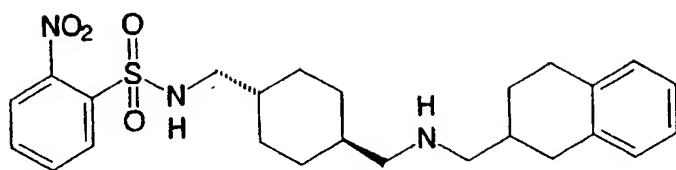
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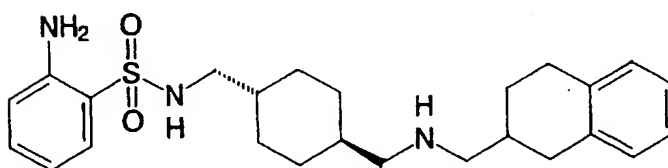


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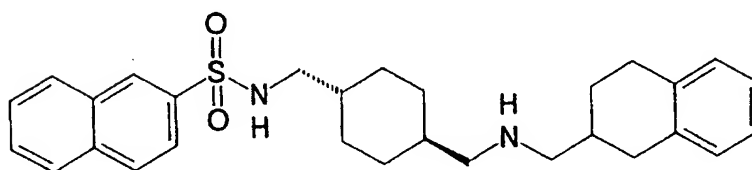
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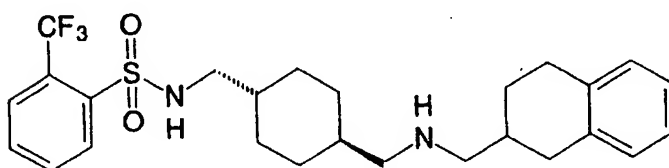


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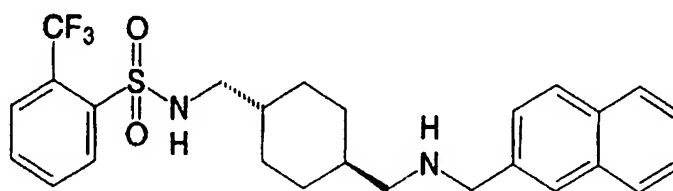
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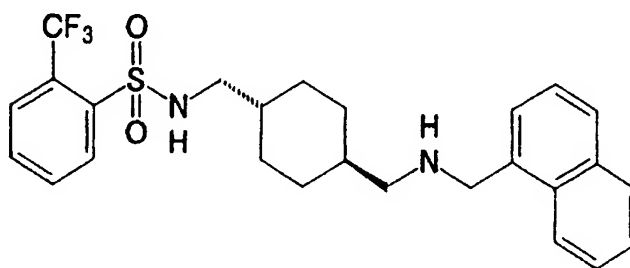
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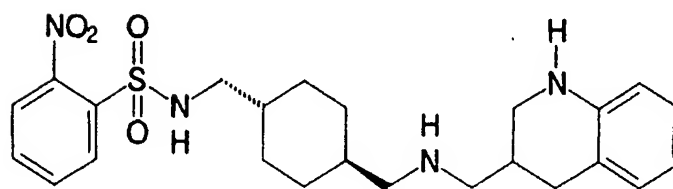


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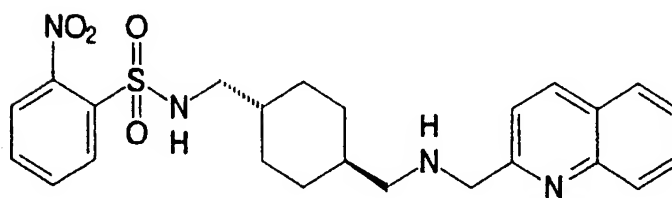
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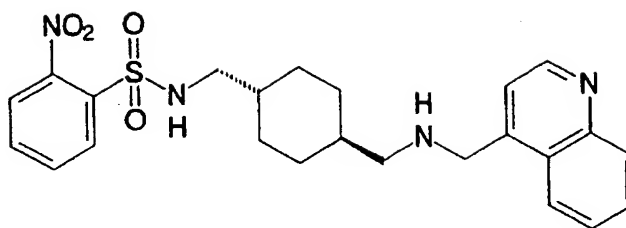
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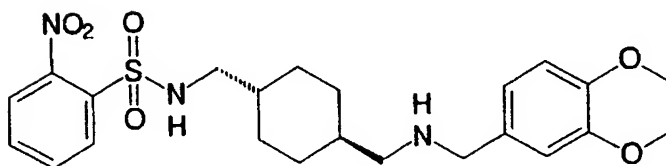
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or

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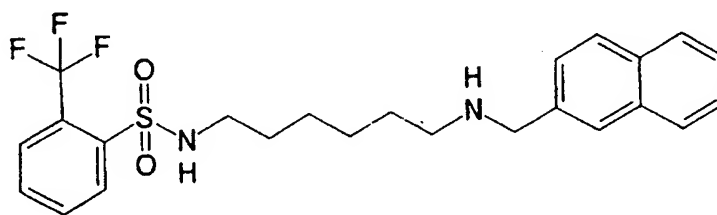


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10. A compound of claim 6, wherein L is C<sub>3</sub>-alkyl or C<sub>7</sub>-alkyl.

11. A compound of claim 10 having the structure:

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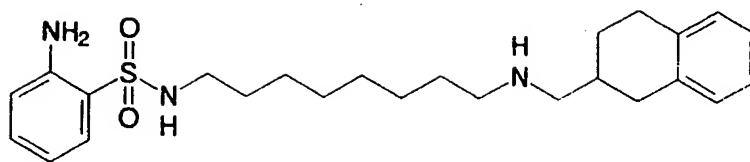


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or

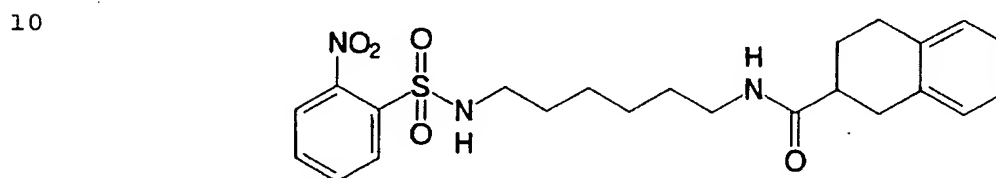
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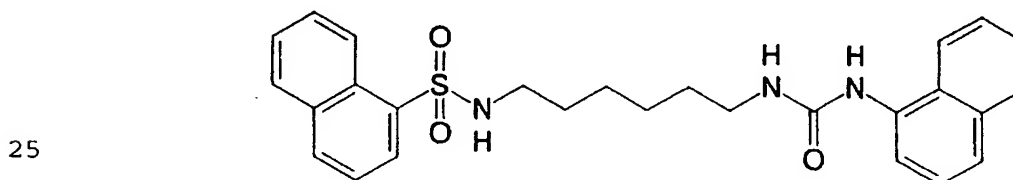
12. A compound of claim 10, wherein K is  
5  $-\text{CH}_2-\text{NR}_{10}-\text{CO}-(\text{CH}_2)_j-$ .

13. A compound of claim 12 having the structure:



14. A compound of claim 10, wherein K is  
15  $-\text{CH}_2-\text{NH}-\text{CO}-\text{NH}-(\text{CH}_2)_j-$ .

- 20 15. The compound of claim 14 having the structure:

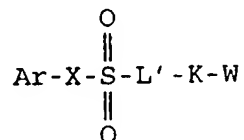


- 25  
30 16. A method of modifying feeding behavior of a subject which comprises administering to the subject an

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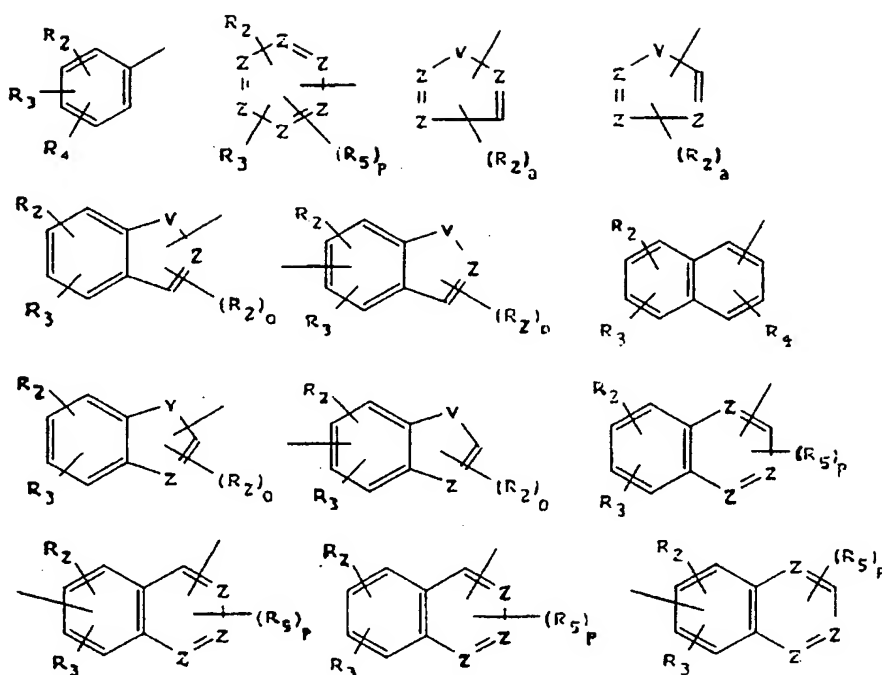
amount of a compound effective to decrease the consumption of food by the subject so as to thereby modify feeding behavior of the subject, wherein the compound has the structure:

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wherein Ar is



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wherein each Z is independently N or C;

wherein each Y is independently N or C;

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wherein p is an integer from 0 to 2;

wherein o is an integer from 0 to 1 and a is an integer from 0 to 3;

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wherein V is S, O, N, or  $NR_5$ ;

wherein X is a single bond or  $-NH-$ ;

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5 wherein each  $R_2$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_2\text{-C}_4$  alkenyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ;  $\text{SO}_2\text{N}(\text{R}_5)_2$ ; phenoxy; phenyl; pyridyl; thiophenyl; naphthyl; phthalimide;  $\text{C}_5\text{-C}_7$  lactam,  $\text{C}_5\text{-C}_7$  cyclic imide,  $\text{C}_5\text{-C}_7$  cyclic amino; wherein the phthalimide, lactam, cyclic imide, or cyclic amine is linked by nitrogen; and wherein the phenoxy, phenyl, pyridyl, thiophenyl, naphthyl, phthalimide, lactam, cyclic imide, or cyclic amine is substituted with H, F, Cl, Br, I,  $\text{CF}_3$ ,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  alkoxy,  $\text{C}_1\text{-C}_4$  alkylthio, or  $\text{NO}_2$ ;

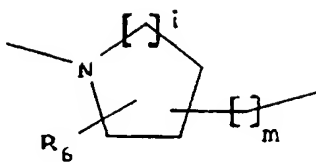
15 wherein each  $R_3$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_2\text{-C}_4$  alkenyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ;  $\text{SO}_2\text{N}(\text{R}_5)_2$ ; or  $R_2$  and  $R_3$  present on adjacent carbon atoms can constitute  $\text{C}_5\text{-C}_7$  cycloalkyl,  $\text{C}_5\text{-C}_7$  heterocycloalkyl or  $\text{C}_5\text{-C}_7$  heteroaryl;

25 wherein each  $R_4$  is independently H; F; Cl; Br; I;  $\text{NO}_2$ ; OH;  $\text{C}_1\text{-C}_4$  alkyl;  $\text{C}_1\text{-C}_4$  alkoxy;  $\text{C}_1\text{-C}_4$  hydroxyalkyl;  $\text{C}_1\text{-C}_4$  methoxyalkyl;  $\text{C}_1\text{-C}_4$  monohaloalkyl;  $\text{C}_1\text{-C}_4$  polyhaloalkyl;  $\text{N}(\text{R}_5)_2$ ;  $\text{NHCOR}_5$ ;  $\text{N}(\text{COR}_5)_2$ ;  $\text{NHCO}_2\text{R}_5$ ;  $\text{NHCONHR}_5$ ;  $\text{NHSO}_2\text{R}_5$ ;  $\text{N}(\text{SO}_2\text{R}_5)_2$ ;  $\text{CO}_2\text{R}_5$ ;  $\text{CON}(\text{R}_5)_2$ ; or  $\text{SO}_2\text{N}(\text{R}_5)_2$ ;

30 wherein each  $R_5$  is independently H;  $\text{C}_1\text{-C}_3$  alkyl;  $\text{C}_1\text{-C}_3$  monohaloalkyl; or  $\text{C}_1\text{-C}_3$  polyhaloalkyl;

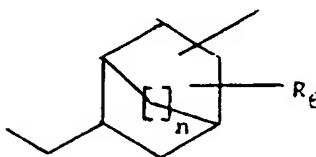
35 wherein  $L'$  is  $-\text{NR}_1\text{-L-}$  or

-150-

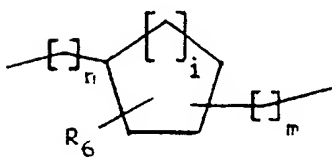


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wherein L is C<sub>3</sub>-C<sub>9</sub> alkyl; C<sub>3</sub>-C<sub>9</sub> alkenyl; C<sub>3</sub>-C<sub>9</sub> alkynyl;

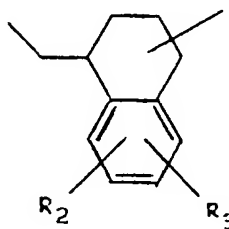


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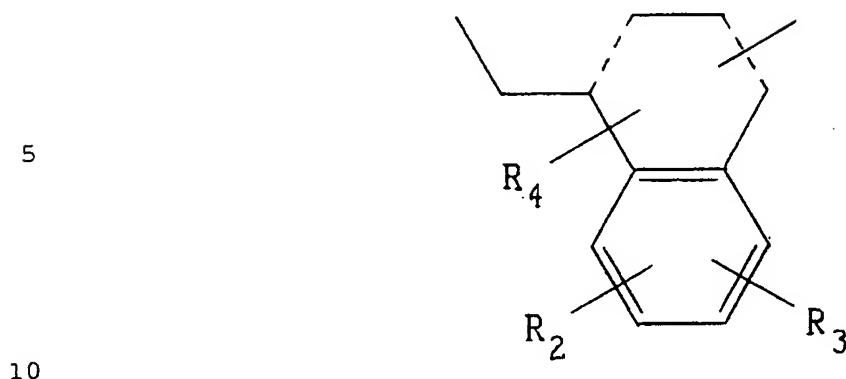
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or

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wherein  $R_1$  is H; or  $C_1$ - $C_3$  straight chained alkyl;

wherein the alkyl, alkenyl or alkynyl is substituted with H,  $OR_5$ , CN,  $C_1$ - $C_6$  alkyl,  $CH_2OR_5$ ,  $CON(R_5)_2$ ,  $CO_2R_5$ , phenyl, pyridyl, thiophenyl or naphthyl;

wherein one dashed line is a double bond and the other dashed line is a single bond;

wherein each  $R_6$  is independently H; CN;  $OR_5$ ;  $C_1$ - $C_5$  alkyl;  $CH_2OR_5$ ;  $CON(R_5)_2$ ;  $CO_2R_5$ ; phenyl; pyridyl; thiophenyl or naphthyl; wherein the phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio, or  $NO_2$ ;

wherein  $i$  is an integer from 1 to 4; wherein  $n$  is an integer from 0 to 3; wherein  $m$  is an integer from 0 to 3;

wherein  $K$  is  $-CH_2-NR_{10}-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-(CH_2)_j-$ ;  $-CH_2-NH-CO-NH-(CH_2)_j-$ ;  $-CO-NH-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CS-(CH_2)_j-$ ;  $-CH_2-NH-CS-NH-$

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$(\text{CH}_2)_1-$ ;  $-\text{CS}-\text{NH}-\text{CHR}_7-(\text{CH}_2)_j-$ ;  $-\text{CH}_2-\text{NR}_{10}-\text{CS}-\text{CHR}_7-(\text{CH}_2)_j$ ;  
or  $-\text{CH}_2-\text{N}=\text{CSR}_1-\text{NH}-(\text{CH}_2)_j$ ;

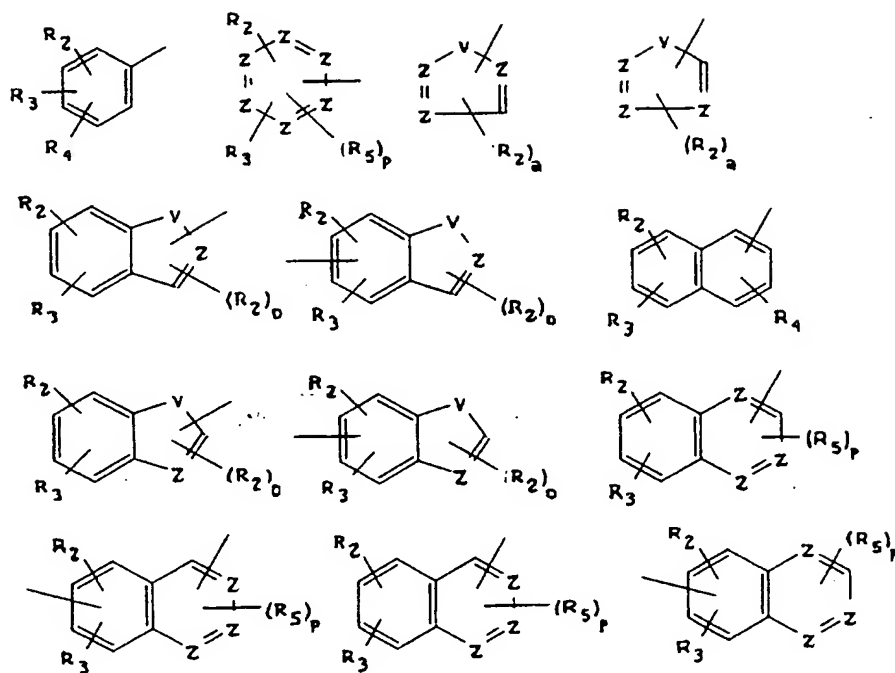
wherein  $j$  is an integer from 0 to 3;

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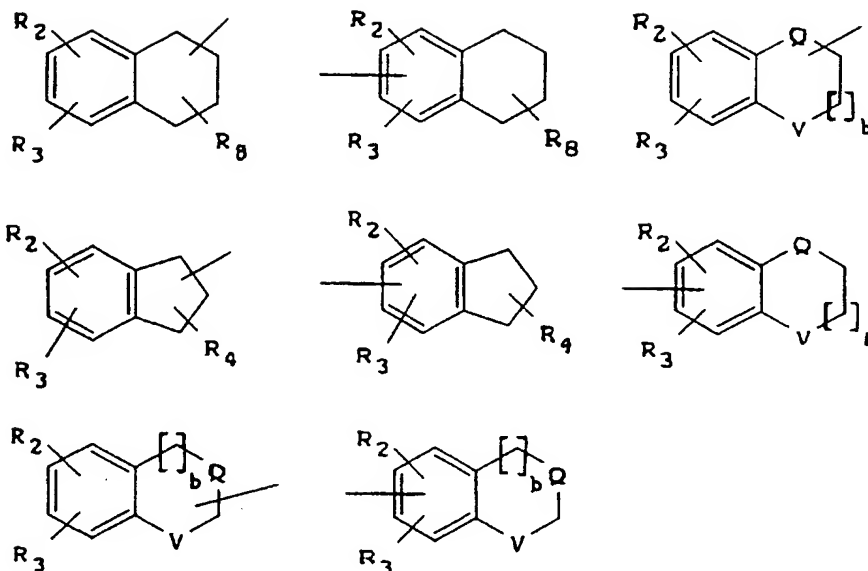
wherein  $R_7$  is H;  $\text{C}_1-\text{C}_6$  alkyl;  $\text{CH}_2\text{OR}_5$ ;  $(\text{CH}_2)_p\text{NHCO}_2\text{R}_5$ ;  
 $(\text{CH}_2)_p\text{NHSO}_2\text{R}_5$ ;  $\text{CH}_2\text{N}(\text{R}_{11})_2$ ; phenyl; pyridyl; thiophenyl;  
or naphthyl;



wherein W is



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wherein Q is O; S; N; NR<sub>9</sub>; or C(R<sub>5</sub>)<sub>2</sub>;

5 wherein b is an integer from 1 to 2;

wherein R<sub>8</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; =O; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; or SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;

10

wherein R<sub>9</sub> is H; C<sub>1</sub>-C<sub>3</sub> alkyl; COR<sub>5</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>;

15

wherein R<sub>10</sub> is H; or C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein R<sub>11</sub> is H; COR<sub>5</sub>; COR<sub>12</sub>; SO<sub>2</sub>R<sub>5</sub>; SO<sub>2</sub>R<sub>12</sub>; and

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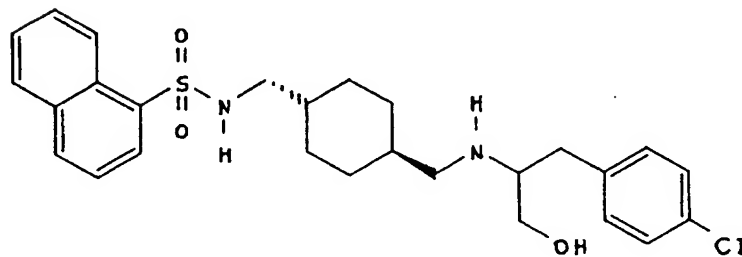
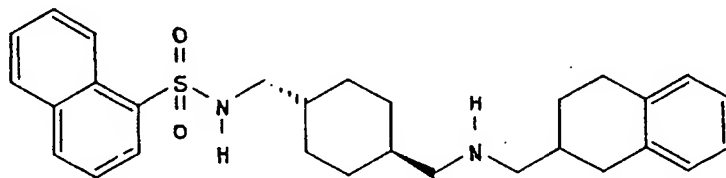
wherein  $R_{12}$  is phenoxy; phenyl, pyridyl; thiophenyl; or naphthyl; wherein the phenoxy, phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1-C_4$  alkyl,  $C_1-C_4$  alkoxy,  $C_1-C_4$  alkylthio,  $NO_2$ , phenyl, pyridyl or thiophenyl;

or a pharmaceutically acceptable salt thereof.

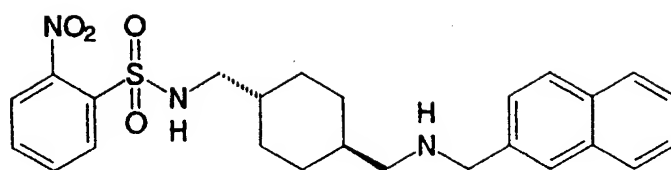
17. The method of claim 16, wherein the compound is administered in combination with food.

18. The method of claim 16, wherein the subject is a vertebrate, a mammal, a human or a canine.

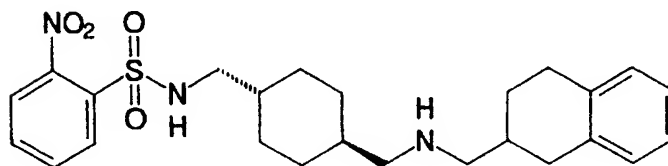
19. The method of claim 16, wherein the compound has the structure:



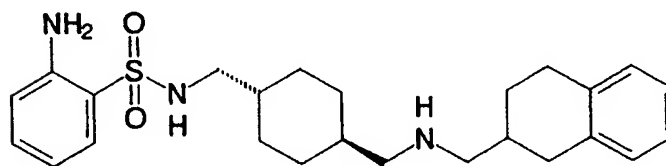
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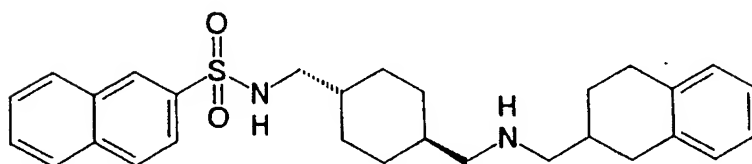


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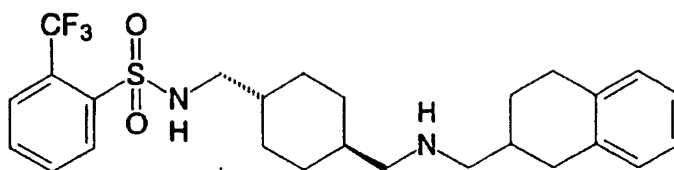
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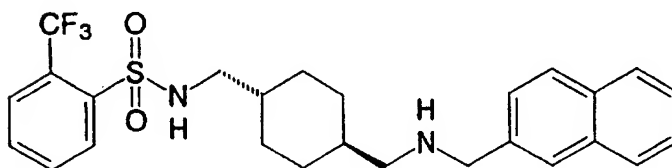
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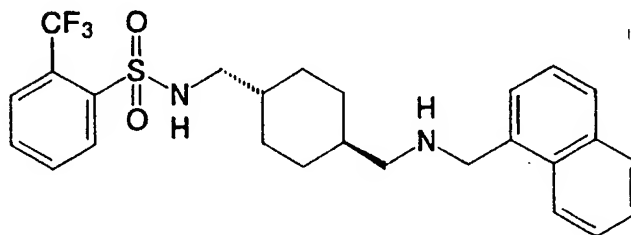
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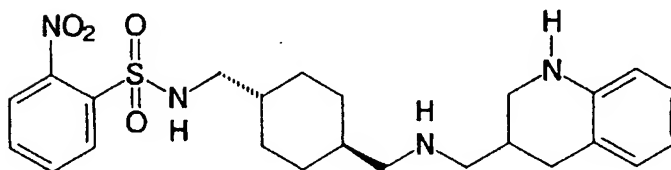


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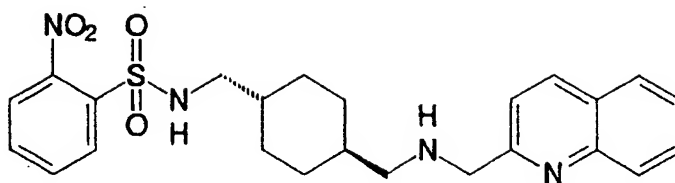
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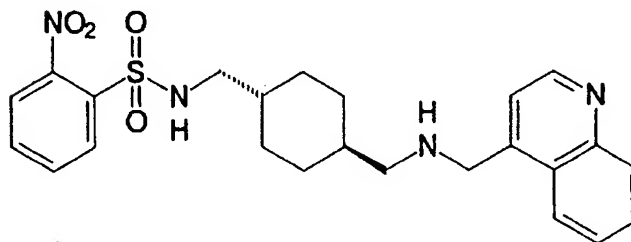
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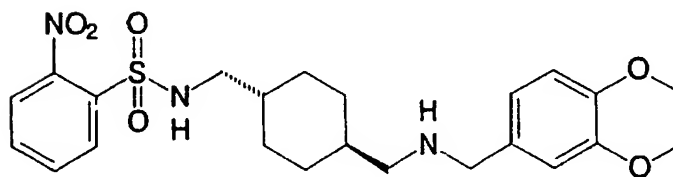


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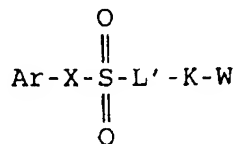
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20. A method of treating a feeding disorder in a subject which comprises administering to the subject an amount of a compound effective to decrease the consumption of food by the subject, wherein the compound has the structure:

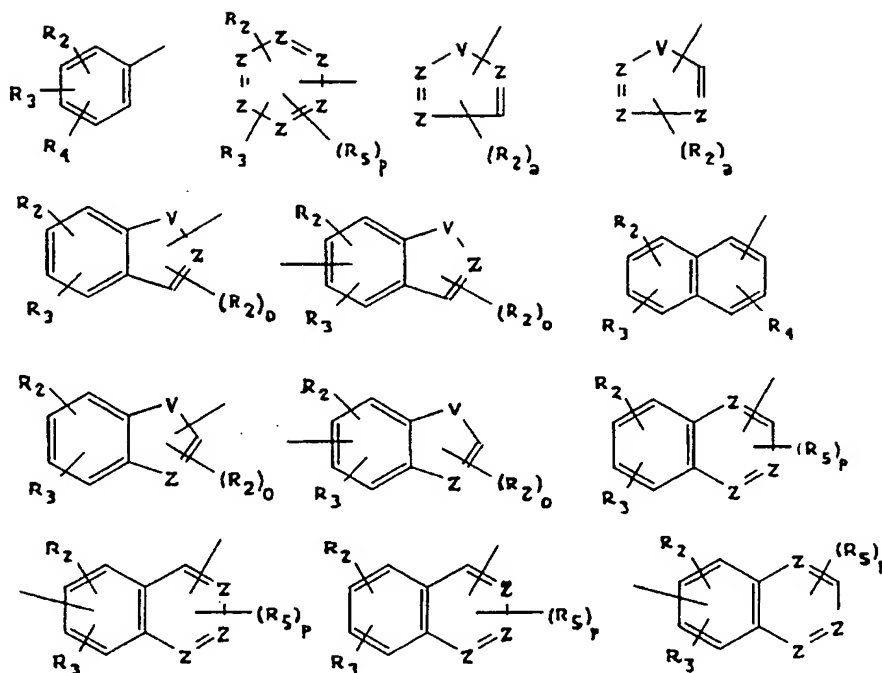
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wherein Ar is

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wherein each Z is independently N or C;

wherein each Y is independently N or C;

5 wherein p is an integer from 0 to 2;

wherein o is an integer from 0 to 1 and a is an integer from 0 to 3;

10 wherein V is S, O, N, or NR<sub>5</sub>;

wherein X is a single bond or -NH-;

15 wherein each R<sub>2</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>4</sub> alkenyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>;

NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;  
 phenoxy; phenyl; pyridyl; thiophenyl; naphthyl;  
 phthalimide; C<sub>5</sub>-C<sub>7</sub> lactam, C<sub>5</sub>-C<sub>7</sub> cyclic imide, C<sub>5</sub>-C<sub>7</sub>  
 cyclic amino; wherein the phthalimide, lactam,  
 5 cyclic imide, or cyclic amine is linked by nitrogen;  
 and wherein the phenoxy, phenyl, pyridyl,  
 thiophenyl, naphthyl, phthalimide, lactam, cyclic  
 imide, or cyclic amine is substituted with H, F, Cl,  
 Br, I, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio,  
 10 or NO<sub>2</sub>;

wherein each R<sub>3</sub> is independently H; F; Cl; Br; I;  
 NO<sub>2</sub>; OH; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>2</sub>-C<sub>4</sub> alkenyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub>  
 hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl;  
 15 C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>;  
 NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;  
 or R<sub>2</sub> and R<sub>3</sub> present on adjacent carbon atoms can  
 constitute C<sub>5</sub>-C<sub>7</sub> cycloalkyl, C<sub>5</sub>-C<sub>7</sub> heterocycloalkyl or  
 C<sub>5</sub>-C<sub>7</sub> heteroaryl;

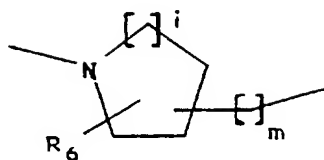
20 wherein each R<sub>4</sub> is independently H; F; Cl; Br; I;  
 NO<sub>2</sub>; OH; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl;  
 C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub>  
 polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>;  
 25 NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; or  
 SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;

wherein each R<sub>6</sub> is independently H; C<sub>1</sub>-C<sub>3</sub> alkyl; C<sub>1</sub>-C<sub>3</sub>  
 monohaloalkyl; or C<sub>1</sub>-C<sub>3</sub> polyhaloalkyl;

30 wherein L' is -NR<sub>1</sub>-L- or

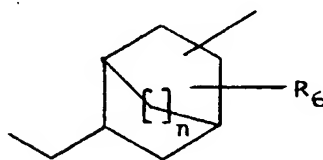


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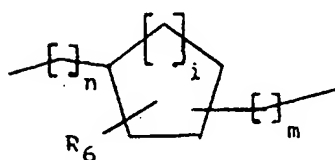


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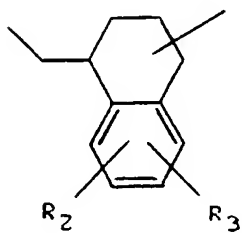
wherein L is C<sub>3</sub>-C<sub>6</sub> alkyl; C<sub>3</sub>-C<sub>6</sub> alkenyl; C<sub>3</sub>-C<sub>6</sub> alkynyl;



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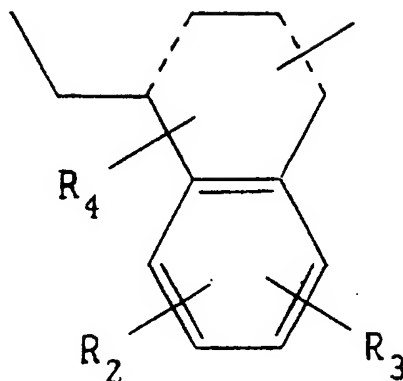
or

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wherein  $R_1$  is H; or  $C_1$ - $C_3$  straight chained alkyl;

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wherein the alkyl, alkenyl or alkynyl is substituted with H,  $OR_5$ , CN,  $C_1$ - $C_6$  alkyl,  $CH_2OR_5$ ,  $CON(R_5)_2$ ,  $CO_2R_5$ , phenyl, pyridyl, thiophenyl or naphthyl;

20

wherein one dashed line is a double bond and the other dashed line is a single bond;

25

wherein each  $R_6$  is independently H; CN;  $OR_5$ ;  $C_1$ - $C_5$  alkyl;  $CH_2OR_5$ ;  $CON(R_5)_2$ ;  $CO_2R_5$ ; phenyl; pyridyl; thiophenyl or naphthyl; wherein the phenyl, pyridyl, thiophenyl or naphthyl is substituted with H, F, Cl, Br, I,  $CF_3$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkylthio, or  $NO_2$ ;

30

wherein  $i$  is an integer from 1 to 4; wherein  $n$  is an integer from 0 to 3; wherein  $m$  is an integer from 0 to 3;

wherein  $K$  is  $-CH_2-NR_{10}-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-(CH_2)_j-$ ;  $-CH_2-NH-CO-NH-(CH_2)_j-$ ;  $-CO-NH-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CO-CHR_7-(CH_2)_j$ ;  $-CH_2-NR_{10}-CS-(CH_2)_j-$ ;  $-CH_2-NH-CS-NH-$

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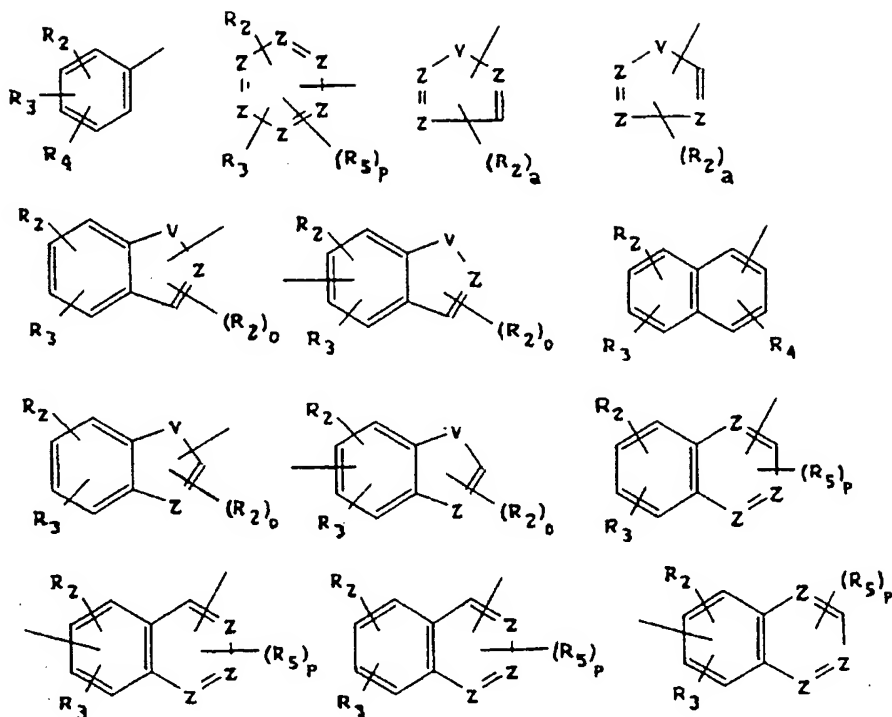
$(CH_2)_i-$ ;  $-CS-NH-CHR_7-(CH_2)_j-$ ;  $-CH_2-NR_{10}-CS-CHR_7-(CH_2)_j$ ;  
or  $-CH_2-N=CSR_1-NH-(CH_2)_j$ ;

wherein  $j$  is an integer from 0 to 3;

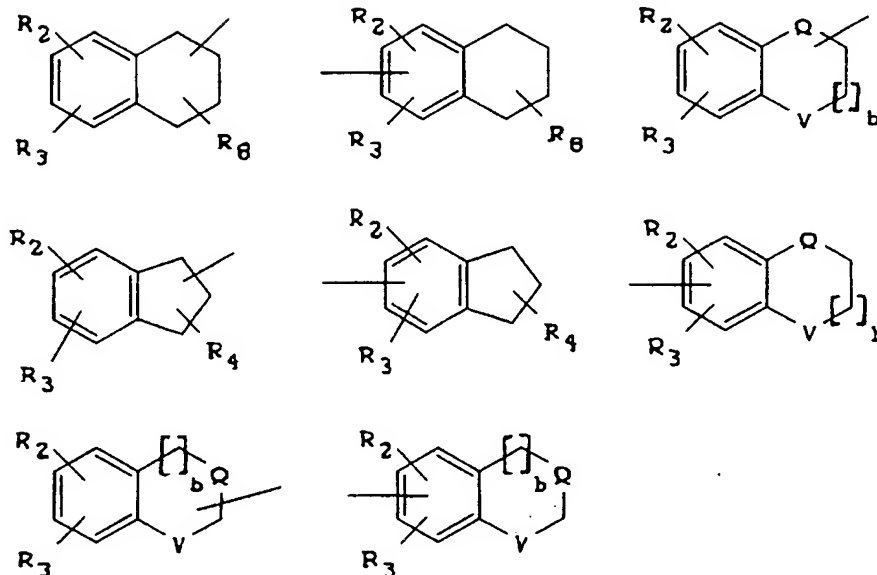
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wherein  $R_7$  is H;  $C_1-C_6$  alkyl;  $CH_2OR_5$ ;  $(CH_2)_pNHCO_2R_5$ ;  
 $(CH_2)_pNHCO_2R_5$ ;  $CH_2N(R_{11})_2$ ; phenyl; pyridyl; thiophenyl;  
or naphthyl;

wherein W is



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wherein Q is O; S; N; NR<sub>9</sub>; or C(R<sub>5</sub>)<sub>2</sub>;

5 wherein b is an integer from 1 to 2;

wherein R<sub>6</sub> is independently H; F; Cl; Br; I; NO<sub>2</sub>; OH; =O; C<sub>1</sub>-C<sub>4</sub> alkyl; C<sub>1</sub>-C<sub>4</sub> alkoxy; C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl; C<sub>1</sub>-C<sub>4</sub> methoxyalkyl; C<sub>1</sub>-C<sub>4</sub> monohaloalkyl; C<sub>1</sub>-C<sub>4</sub> polyhaloalkyl; N(R<sub>5</sub>)<sub>2</sub>; NHCOR<sub>5</sub>; N(COR<sub>5</sub>)<sub>2</sub>; NHCO<sub>2</sub>R<sub>5</sub>; 10 NHCONHR<sub>5</sub>; NHSO<sub>2</sub>R<sub>5</sub>; N(SO<sub>2</sub>R<sub>5</sub>)<sub>2</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>; or SO<sub>2</sub>N(R<sub>5</sub>)<sub>2</sub>;

15 wherein R<sub>9</sub> is H; C<sub>1</sub>-C<sub>3</sub> alkyl; COR<sub>5</sub>; CO<sub>2</sub>R<sub>5</sub>; CON(R<sub>5</sub>)<sub>2</sub>;

wherein R<sub>10</sub> is H; or C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein R<sub>11</sub> is H; COR<sub>5</sub>; COR<sub>12</sub>; SO<sub>2</sub>R<sub>5</sub>; SO<sub>2</sub>R<sub>12</sub>; and

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wherein R<sub>12</sub> is phenoxy; phenyl, pyridyl; thiophenyl;  
or naphthyl; wherein the phenoxy, phenyl, pyridyl,  
thiophenyl or naphthyl is substituted with H, F, Cl,  
Br, I, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio,  
NO<sub>2</sub>, phenyl, pyridyl or thiophenyl;

or a pharmaceutically acceptable salt thereof.

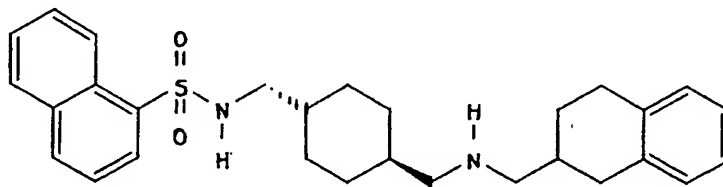
21. The method of claim 20, wherein the feeding disorder  
is obesity or bulimia.

22. The method of claim 21, wherein the subject is a  
vertebrate, a mammal, a human or a canine.

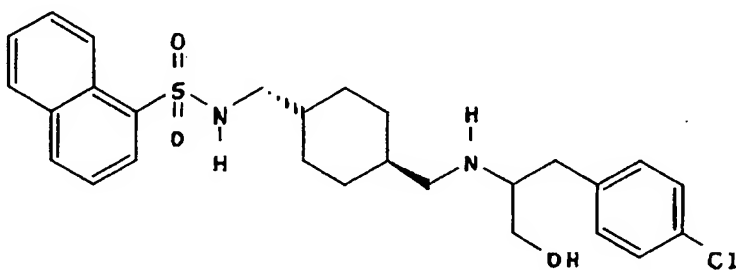
-167-

23. The method of claim 20, wherein the compound has the structure:

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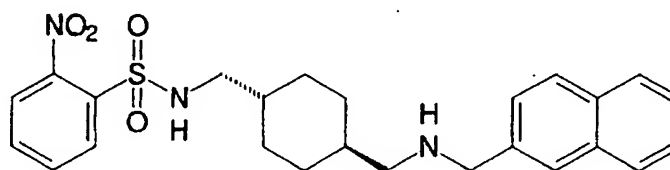


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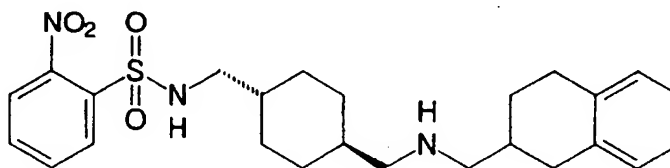


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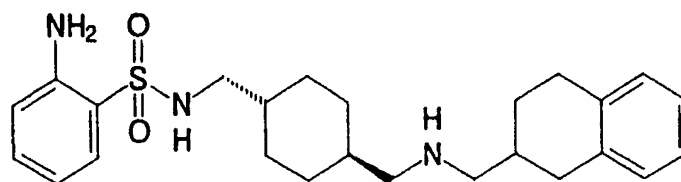
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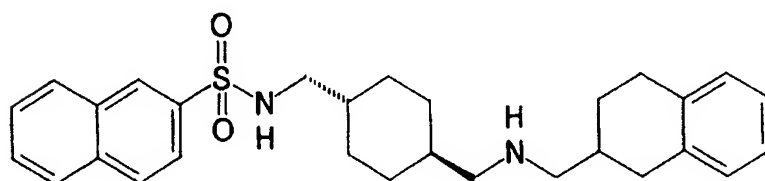
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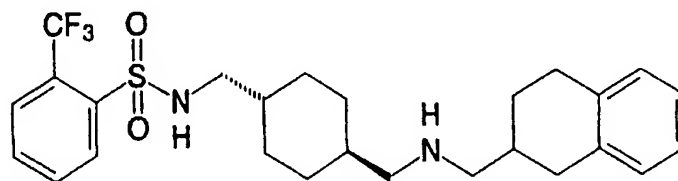
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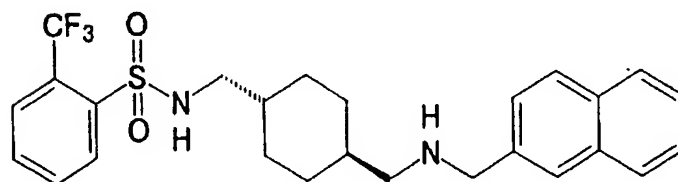
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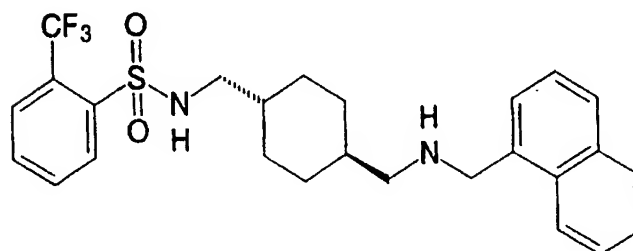


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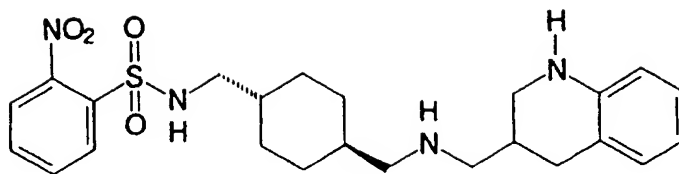
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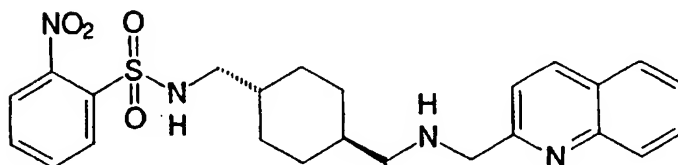
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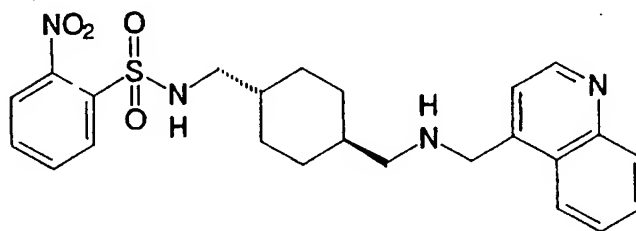
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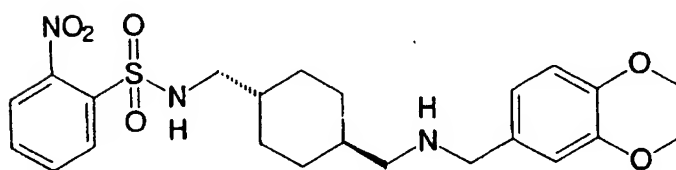
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or

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/19085**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 31/18, 31/335, 31/47; C07C 311/10; C07D 215/12

US CL : 514/311, 452, 602; 546/165, 172; 549/366; 564/87, 90, 92, 94

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/311, 452, 602; 546/165, 172; 549/366; 564/87, 90, 92, 94

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online structure

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,352,705 A (DEANNA, deceased et al.) 04 October 1994, see entire document.	1-23
A	US 5,455,258 A (MACPHERSON et al.) 03 October 1995, see entire document.	1-23

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

31 MARCH 1997

Date of mailing of the international search report

05 MAY 1997

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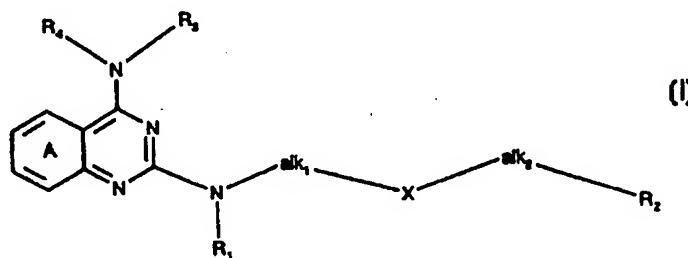
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: QUINAZOLIN-2,4-DIAZIRINES AS NPY RECEPTOR ANTAGONIST

(57) Abstract

The invention relates to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I), in which the variables are as defined and relates to new compounds of formula (I) or a salt thereof, to pharmaceutical compositions, and to the manufacture of new compounds of formula (I) and salts thereof.



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## QUINAZOLIN-2,4-DIAZIRINES AS NPY RECEPTOR ANTAGONIST

Background of the Invention

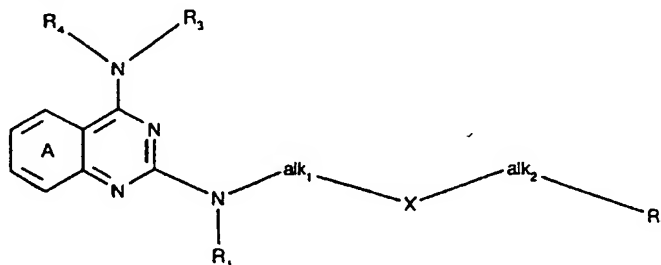
Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family of peptides and is one of the most abundant and widely distributed peptides at the central and peripheral nervous system. NPY acts as a neurotransmitter playing an important role in the regulation of various diseases. Intensive evaluations lead to the finding that multiple NPY receptors are existing being responsible for different physiological and pharmacological activities. Recently, a new NPY receptor subtype has been characterized and cloned, designated as Y5 receptor. It has been demonstrated that the pharmacological function associated with Y5 relates, for example, to obesity and eating disorders. Accordingly, the provision of compounds which act as antagonists of this receptor subtype represents a promisable approach in the regulation of diseases or disorders, such as obesity and eating/food intake disorders.

Summary of the Invention

The invention relates to a method of treatment of disorders and diseases associated with NPY receptor subtype Y5, to pharmaceutical compositions and to new compounds having Y5 antagonistic properties.

Detailed Description of the Invention

The invention relates to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I)



in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R<sub>2</sub> represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, by carbamoyl, or by N-substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X<sub>1</sub>(X<sub>2</sub>)(X<sub>3</sub>) wherein, (a) if X<sub>1</sub> is -CH-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>r</sub>-, or -(CH<sub>2</sub>)<sub>s</sub>-X<sub>4</sub>-CO-(CH<sub>2</sub>)<sub>t</sub>-; or, (b) if X<sub>1</sub> is -N-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -CO-(CH<sub>2</sub>)<sub>u</sub>-; [X<sub>4</sub> being -CH<sub>2</sub>-, -N(R<sub>1</sub>)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X<sub>4</sub> is different from -CH<sub>2</sub>-];

R<sub>3</sub> and R<sub>4</sub>, independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or  
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -S(O)<sub>n</sub>-R;

R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, NR<sub>0</sub>] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents (carbocyclic or heterocyclic) arylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

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wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO<sub>2</sub>-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy; or a pharmaceutically acceptable salt thereof; and relates to new compounds of formula (I) or a salt thereof, to pharmaceutical compositions, and to the manufacture of new compounds of formula (I) and salts thereof.

The compounds of formula (I) can be present as salts, in particular pharmaceutically acceptable salts. If the compounds (I) have, for example, at least one basic centre, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as C<sub>1</sub>-C<sub>4</sub>-alkanecarboxylic acids which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or such as benzoic acid, or with organic sulfonic acids, such as C<sub>1</sub>-C<sub>4</sub>-alkane- or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluenesulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an



additionally present basic centre. The compounds (I) having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, for example, mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed, if a compound of formula comprises e.g. both a carboxy and an amino group. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds (I) or their pharmaceutically acceptable salts, are also included.

(Carbocyclic or heterocyclic) aryl in (carbocyclic or heterocyclic) aryl or aryloxy, respectively, represents, for example, phenyl, biphenyl, naphthyl or an appropriate 5- or 6-membered and monocyclic radical or an appropriate bicyclic heteroaryl radical which, in each case, have up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom. Appropriate 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered radicals are in particular pyridyl. Appropriate bicyclic heterocyclic aryls are, for example, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isoquinolinyl, or quinazolinyl. Appropriate aromatic radicals, including ring A, are radicals which may be monosubstituted or polysubstituted, for example di- or trisubstituted, for example by identical or different radicals, for example selected from the group as given above. Preferred substituents of corresponding aryl radicals (including of ring A) are, for example, halogen, lower alkyl, halo-lower alkyl, lower alkoxy, oxy-lower alkylene-oxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

(Carbocyclic or heterocyclic) aroyl is in particular benzoyl, naphthoyl, furoyl, thenoyl, or pyridoyl.

(Carbocyclic or heterocyclic) aryl-lower alkanoyl in (carbocyclic or heterocyclic) aryl-lower alkanoyloxy or (carbocyclic or heterocyclic) aryl-lower alkanoyl is in particular phenyl-lower alkanoyl, naphthyl-lower alkanoyl, or pyridyl-lower alkanoyl.

(Carbocyclic or heterocyclic) aryl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-lower alkyl.

(Carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl is in particular phenyl-, naphthyl- or pyridyl-lower alkoxy.

(Carbocyclic or heterocyclic) arylene represents, in particular, phenylene, naphthylene, thiophenylene, furylene, pyridylene which may be substituted, for example, as indicated for benzo ring A or preferably unsubstituted.

Lower alkyl which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl, amino-lower alkyl, or N- or N,N- substituted amino-lower alkyl.

An amino group which is mono-substituted by lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl is in particular lower alkylamino, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-amino, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-loweralkyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkylamino.

An amino group which is, independently of one another, di-substituted by lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl is in particular di-lower alkylamino, di-C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-amino, di-(C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino, lower alkyl-C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-amino, lower alkyl-(C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl)-amino, lower alkyl-(phenyl-,

naphthyl-, furyl-, thienyl-, or pyridyl)-amino, lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino.

Lower alkyl which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, NR<sub>0</sub>, the integer n being 0, 1 or 2 and R<sub>0</sub> being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO<sub>3</sub>H, -SO<sub>2</sub>-R and R being lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl] is in particular carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, lower alkoxy-lower alkoxy-carbonyl-lower alkyl, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, or corresponding N- or N,N-substituted carbamoyl-lower alkyl.

Lower alkoxy which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy, amino-lower alkoxy, or corresponding N- or N,N- substituted amino-lower alkoxy.

Lower alkoxy which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, NR<sub>0</sub>, the integer n being 0, 1 or 2 and R<sub>0</sub> being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO<sub>3</sub>H, -SO<sub>2</sub>-R and R being lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-

lower alkyl] is in particular carboxy-lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, lower alkoxy-lower alkoxy-carbonyl-lower alkoxy, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxy-carbonyl-lower alkoxy, carbamoyl-lower alkoxy, N- or N,N-substituted carbamoyl-lower alkoxy.

Substituted lower alkyl or lower alkoxy, respectively, is mono- or poly-substituted, e.g. di- or tri-substituted.

The group of formula  $-N(R_3)(R_4)$  in which  $R_3$  and  $R_4$  together represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring represents, for example, lower alkylene-phenylene-lower alkylene-amino, such as 3,4-dihydro-1*H*-isoquinolin-2-yl.

The general definitions used above and below, unless defined differently, have the following meanings:

The expression "lower" means that corresponding groups and compounds, in each case, in particular comprise not more than 7, preferably not more than 4, carbon atoms.

Halogen is in particular halogen of atomic number not more than 35, such as fluorine, chlorine or bromine, and also includes iodine.

Lower alkyl is in particular  $C_1$ - $C_7$ -alkyl, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and also includes corresponding pentyl, hexyl and heptyl radicals.  $C_1$ - $C_4$ -alkyl is preferred.

Lower alkenyl is in particular  $C_3$ - $C_7$ -alkenyl and is, for example, 2-propenyl or 1-, 2- or 3-butenyl.  $C_3$ - $C_5$ -alkenyl is preferred.

Lower alkynyl is in particular  $C_3$ - $C_7$ -alkynyl and is preferably propargyl.

Lower alkoxy is in particular  $C_1$ - $C_7$ -alkoxy and is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy and also includes corresponding pentyloxy, hexyloxy and heptyloxy radicals.  $C_1$ - $C_4$ -

alkoxy is preferred.

Lower alkenyloxy is in particular C<sub>3</sub>-C<sub>7</sub>-alkenyloxy, preferably allyloxycarbonyl, while lower alkynyloxy is in particular C<sub>3</sub>-C<sub>5</sub>-alkynyloxy, such as propargyloxy.

Oxy-lower alkylene-oxy is in particular oxy-C<sub>1</sub>-C<sub>4</sub>-alkylene-oxy, preferably oxy-methylene-oxy or oxy-ethylene-oxy.

Lower alkanoyloxy is in particular C<sub>2</sub>-C<sub>7</sub>-alkanoyloxy, such as acetyloxy, propionyloxy, butyryloxy, isobutyryloxy or pivaloyloxy. C<sub>2</sub>-C<sub>5</sub>-alkanoyloxy is preferred.

Lower alkanoyl is in particular C<sub>2</sub>-C<sub>7</sub>-alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C<sub>2</sub>-C<sub>5</sub>-alkanoyl is preferred.

Naphthoyl is 1- or 2-naphthoyl, furoyl 2- or 3-furoyl, thenoyl 2- or 3-thenyl, and pyridoyl 2-, 3-, or 4-pyridoyl.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-lower alkyl is in particular C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, in particular C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-C<sub>1</sub>-C<sub>2</sub>-alkyl. Preferred is cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkoxy is, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy. Cyclopentyloxy and cyclohexyloxy are preferred.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-lower alkoxy is in particular C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, in particular C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-C<sub>1</sub>-C<sub>2</sub>-alkoxy. Preferred is cyclopropylmethoxy, cyclopentylmethoxy or cyclohexylmethoxy.

Lower alkylene is in particular C<sub>1</sub>-C<sub>7</sub>-alkylene, in particular C<sub>1</sub>-C<sub>5</sub>-alkylene, and is straight-chain or branched and is in particular methylene, ethylene, propylene and

butylene and also 1,2-propylene, 2-methyl-1,3-propylene, 3-methyl-1,5-pentylene and 2,2-dimethyl-1,3-propylene. C<sub>3</sub>-C<sub>5</sub>-alkylene is preferred. In case of alk<sub>1</sub> or alk<sub>2</sub>, respectively, lower alkylene preferably is -(CH<sub>2</sub>)<sub>p</sub>- the integer p being 1-3. Lower alkylene in an substituted amino group preferably is 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, 2-methyl-1,3-propylene, or 2-methyl-butylene, or 3-methyl-1,5-pentylene.

Amino which is di-substituted by lower alkylene is in particular C<sub>3</sub>-C<sub>7</sub>-alkyleneamino, preferably 1-azidino, 1-pyrrolidino or 1-piperidino.

Amino which is di-substituted by lower alkylene which is interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub> is in particular morpholino, thiomorpholino or the mono- or di-oxide thereof, or 4-R<sub>0</sub>-piperazino.

Lower alkanesulfonyl is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl, preferably ethoxyethoxycarbonyl, methoxyethoxycarbonyl and isopropoxyethoxycarbonyl.

Lower alkoxycarbonyl is in particular C<sub>2</sub>-C<sub>8</sub>-alkoxycarbonyl and is, for example, methoxy-, ethoxy-, propyloxy- or pivaloyloxy-carbonyl. C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl is preferred.

Lower alkoxy-lower alkoxy-carbonyl is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl and is, for example, methoxy- or ethoxy-ethoxy-alkoxycarbonyl.

Hydroxy-lower alkyl is in particular hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl. Furthermore, hydroxy-lower alkyl may exhibit two hydroxy groups, such as 3-hydroxy-1-hydroxymethyl-propyl.

Hydroxy-lower alkoxy is in particular hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

Lower alkoxy-lower alkoxy is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy and is, for example, (m)ethoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2-n-propyloxyethoxy or ethoxymethoxy.

Amino which is di-substituted by lower alkylene and is condensed at two adjacent carbon atoms with a benzene ring is in particular C<sub>2</sub>-C<sub>6</sub>-cycloalkylenemino which is condensed at two adjacent carbon atoms with a benzene ring. Preferred is indolin-1-yl or 1,2,3,4-tetrahydro-quinolin-1-yl.

Halo-lower alkyl is in particular halo-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as trifluoromethyl, 1,1,2-trifluoro-2-chloroethyl or chloromethyl.

Halo-lower alkoxy is in particular halo-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as trifluoromethoxy, 1,1,2-trifluoro-2-chloroethoxy or chloromethoxy.

Phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl is in particular phenyloxy-, naphthyloxy- or pyridyloxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as phenoxy-methyl, 2-phenoxy-ethyl, 1- or 2-naphthyloxy-methyl, or 2-, 3-, or 4-pyridyloxy-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as phenyl-methyl, 2-phenyl-ethyl, 1- or 2-naphthyl-methyl, or 2-, 3-, or 4-pyridyl-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy is in particular phenyl-, naphthyl- or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as phenyl-methoxy, 2-phenyl-ethoxy, 1- or 2-naphthyl-methoxy, or 2-, 3-, or 4-pyridyl-methoxy.

Naphthyl is in particular 1- or 2-naphthyl; furyl 2- or 3-furyl; thienyl 2- or 3-thienyl; pyridyl 2-, 3- or 4-pyridyl, indolyl e.g. 1-, 2-, 3- or 5-indolyl, indazolyl e.g. 6-1(H)-indazolyl, benzofuranyl e.g. 2-, 3- or 5-benzofuranyl, benzothienyl e.g. 2-, 3-, or 5-benzothienyl, benzimidazolyl e.g. 1-, 2- or 5-benzimidazolyl, quinolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinolinyl, isoquinolinyl e.g. 1-, 3-, 4-, or 6-isoquinolinyl, or quinazolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl.

Amino-lower alkyl is in particular amino-C<sub>1</sub>-C<sub>7</sub>-alkyl, preferably amino-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as aminomethyl, 2-aminoethyl or 3-aminopropyl.

Lower alkylamino is in particular C<sub>1</sub>-C<sub>7</sub>-alkylamino and is, for example, methyl-, ethyl-, n-propyl- and isopropyl-amino. C<sub>1</sub>-C<sub>4</sub>-alkylamino is preferred.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-amino is in particular C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-amino and is, for example, cyclopropyl-, cyclopentyl- and cyclohexyl-amino.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-lower alkylamino is in particular C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>7</sub>-alkylamino and is, for example, cyclopropylmethyl-amino or cyclohexylmethyl-amino. C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino is preferred.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl-amino is in particular phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkyl-amino, preferably benzyl-amino, 2-phenethyl-amino, 1- or 2-naphthylmethyl-amino, or 2-, 3-, or 4-pyridylmethyl-amino.

Di-lower alkylamino is in particular di-C<sub>1</sub>-C<sub>4</sub>-alkylamino, such as dimethyl-, diethyl-, di-n-propyl-, methylpropyl-, methylethyl-, methylbutyl-amino and dibutylamino.

Di-C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-amino is in particular di-C<sub>3</sub>-C<sub>6</sub>-cycloalkylamino, preferably cyclopropylamino, cyclopentylamino or cyclohexylamino.

Di-(C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl)-amino is in particular di-(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl)-amino, preferably cyclopropylmethyl-amino, cyclopentylmethyl-amino or cyclohexylmethyl-amino.

Di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkyl)-amino, preferably di-benzyl-amino, di-(2-phenethyl)-amino, di-(1- or 2-naphthylmethyl)-amino, or di-(2-, 3-, or 4-pyridylmethyl)-amino.

Lower alkyl-C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-amino is in particular C<sub>1</sub>-C<sub>4</sub>-alkyl-C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-amino, preferably methyl-cyclopropyl-amino, methyl-cyclopentyl-amino or methyl-cyclohexyl-amino.



Lower alkyl-(C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl)-amino is in particular C<sub>1</sub>-C<sub>4</sub>-alkyl-(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl)amino, preferably methyl-cyclopropylmethyl-amino, methyl-cyclopentylmethyl-amino or methyl-cyclohexylmethyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino is in particular C<sub>1</sub>-C<sub>4</sub>-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino, such as (m)ethyl-phenyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular C<sub>1</sub>-C<sub>4</sub>-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkyl)-amino, such as (m)ethyl-benzyl-amino or (m)ethyl-(2-phenethyl)-amino.

Carboxy-lower alkyl is in particular carboxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as carboxy-methyl, 2-carboxy-ethyl, or 3-carboxy-propyl.

Lower alkoxy-carbonyl-lower alkyl is in particular C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as (m)ethoxycarbonyl-methyl, 2-(m)ethoxycarbonyl-ethyl or 2-pivaloyl-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkyl is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as 2-methoxy-ethoxycarbonyl-methyl or 2-(2-ethoxy-ethoxycarbonyl)-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxy-carbonyl-lower alkyl is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as benzyloxycarbonyl-methyl or 2-(2-phenethyloxy-carbonyl)-ethyl.

Carbamoyl-lower alkyl is in particular carbamoyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as carbamoyl-methyl, 2-carbamoyl-ethyl or 3-carbamoyl-propyl.

Amino-lower alkoxy is in particular amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as aminomethoxy, 2-aminoethoxy, or 3-amino-propoxy.

Carboxy-lower alkoxy is in particular carboxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as carboxy-methoxy, 2-carboxy-ethoxy, or 3-carboxy-propyloxy.

Lower alkoxy-carbonyl-lower alkoxy is in particular C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as (m)ethoxycarbonyl-methoxy, 2-methoxycarbonyl-ethyl, or 2-(2-ethoxycarbonyl)-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkoxy is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as (m)ethoxymethoxycarbonyl-methoxy, 2-ethoxy-methoxycarbonyl-ethyl, or 2-[(2-ethoxy-ethoxycarbonyl)]-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkoxy is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as benzyloxycarbonyl-methoxy, phenethyloxycarbonyl-methoxy, 2-(benzyloxycarbonyl)-ethoxy, or 2-(2-phenethyloxycarbonyl)-ethoxy.

Carbamoyl-lower alkoxy is in particular carbamoyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as carbamoyl-methoxy, 2-carbamoyl-ethoxy, or 3-carbamoyl-propyloxy.

Phenylene is 1,2-, 1,3 or preferably 1,4-phenylene; naphthylene is in particular 1,2-, 1-3-, 1,4-, 2,4-, 1,5-, or 2,7-naphthylene, furylene is in particular 2,3-, 2,4- or 3,4-furylene, thienylene is in particular 2,3-, 2,4- or 3,4-thienylene, pyridylene is in particular 2,3- or 2,4-pyridylene.

Obesity, for example, is a wide-spread phenomena which e.g. causes a variety of pathological symptoms or influences the overall state of health. Also associated therewith are considerable socio-economic investments and a heavy financial burden for managed health care organisations. The problem to be solved is to present an approach to systemically treat obesity or related diseases or disorders. Surprisingly, it has been manifested that the modulation of the NPY receptor subtype Y5 leads to a control of the eating behavior.

Extensive pharmacological investigations have shown that the compounds (I) and their pharmaceutically acceptable salts, for example, are useful as antagonists of the neuropeptide Y5 receptor subtype.

Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family with wide-spread distribution throughout the mammalian nervous system. NPY and its relatives (peptide YY or PYY, and pancreatic polypeptide or PP) elicit a broad range of physiological effects through activation of at least five G protein-coupled receptor subtypes known as Y1, Y2, Y3, Y4 (or PP), and the "atypical Y1". The role of NPY as the most powerful stimulant of feeding behavior yet described is thought to occur primarily through activation of the hypothalamic "atypical Y1" receptor. This receptor is unique in that its classification is based solely on feeding behavior data, rather than radioligand binding data, unlike the Y1, Y2, Y3, and Y4 (or PP) receptors, each of which are described previously in both radioligand binding and functional assays. <sup>125</sup>I-PYY-based expression cloning technique may be used to isolate a rat hypothalamic cDNA encoding an "atypical Y1" receptor referred to herein as the Y5 subtype. Y5 homolog may be isolated and characterized of from human hippocampus. Protein sequence analysis reveals that the Y5 receptor belongs to the G protein- coupled receptor superfamily. Both the human and rat homolog display  $\leq 42\%$  identity in transmembrane domains with the previously cloned "Y-type" receptors. Rat brain localization studies using in situ hybridization techniques verify the existence of Y5 receptor mRNA in rat hypothalamus. Pharmacological evaluation reveals the following similarities between the Y5 and the "atypical Y1" receptor. 1) Peptides bind to the Y5 receptor with a rank order of potency identical to that described for the feeding response: NPY <sup>3</sup> NPY<sub>2-36</sub> = PYY = [Leu<sup>31</sup>, Pro<sup>34</sup>]NPY >> NPY<sub>13-36</sub>. 2) The Y5 receptor is negatively coupled to cAMP accumulation, as has been proposed for the "atypical Y1" receptor. 3) Peptides activate the Y5 receptor with a rank order of potency identical to that described for the feeding response. 4) The reported feeding "modulator" [D-Trp<sup>32</sup>]NPY binds selectively to the Y5 receptor and subsequently activated the receptor. 5) Both the Y5 and the "atypical Y1" receptors are sensitive to deletions or modifications in the midregion of NPY and related peptide ligands.

The peptide neurotransmitter neuropeptide Y (NPY) is a 36 amino acid member of the pancreatic polypeptide family with widespread distribution throughout the mammalian nervous system. NPY is considered to be the most powerful stimulant of feeding behavior yet described (Clark, J.T., Kalra, P.S., Crowley, W.R., and Kalra, S.P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. *Endocrinology* 115: 427-429, 1984; Levine, A.S., and Morley, J.E. (1984). Neuropeptide Y: A potent inducer of consummatory behavior in rats. *Peptides* 5: 1025-1029; Stanley, B.G., and Leibowitz, S.F.; (1984) Neuropeptide Y: Stimulation of feeding and drinking by injection into the paraventricular nucleus. *Life Sci.* 35: 2635-2642). Direct injection into the hypothalamus of satiated rats, for example,

can increase food intake up to 10-fold over a 4-hour period (Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y<sub>1</sub> receptor mediating this peptide's effect. Peptides 13: 581-587). The role of NPY in normal and abnormal eating behavior, and the ability to interfere with NPY-dependent pathways as a means to appetite and weight control, are areas of great interest in pharmacological and pharmaceutical research (Sahu and Kalra, 1993; Dryden, S., Frankish, H., Wang, Q., and Williams, G. (1994). Neuropeptide Y and energy balance: one way ahead for the treatment of obesity? Eur. J. Clin. Invest. 24: 293-308). Any credible means of studying or controlling NPY-dependent feeding behavior, however, must necessarily be highly specific as NPY can act through at least 5 pharmacologically defined receptor subtypes to elicit a wide variety of physiological functions (Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167). It is therefore vital that knowledge of the molecular biology and structural diversity of the individual receptor subtypes be understood as part of a rational drug design approach to develop subtype selective compounds. A brief review of NPY receptor pharmacology is summarized below and also in Table 1.

TABLE 1: Pharmacologically defined receptors for NPY and related pancreatic polypeptides.

Rank orders of affinity for key peptides (NPY, PYY, PP, [Leu<sup>31</sup>,Pro<sup>34</sup>]NPY, NPY<sub>2-36</sub>, and NPY<sub>13-36</sub>) are based on previously reported binding and functional data (Schwartz, T.W., J. Fuhlendorff, L.L.Kjems, M.S. Kristensen, M. Vervelde, M. O'Hare, J.L. Krstenansky, and B. Bjornholm. (1990). Signal epitopes in the three-dimensional structure of neuropeptide Y. Ann. N.Y. Acad. Sci. 611: 35-47; Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082; Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167; Wahlestedt, C., and D.J. Reis. (1993). Neuropeptide Y-Related Peptides and Their Receptors--Are the Receptors Potential Therapeutic Targets? Ann. Rev. Pharmacol. Tox. 32: 309-352). Missing peptides in the series reflect a lack of published information.

TABLE 1

Receptor	Affinity (pK <sub>i</sub> or pEC <sub>50</sub> )					
	11 to 10	10 to 9	9 to 8	8 to 7	7 to 6	< 6
Y1	NPY PYY [Leu <sup>31</sup> ,Pro <sup>34</sup> ] NPY		NPY <sub>2-36</sub>	NPY <sub>13-36</sub>	PP	
Y2		PYY NPY NPY <sub>2-36</sub>	NPY <sub>13-36</sub>			[Leu <sup>31</sup> ,Pro <sup>34</sup> ] NPY  PP
Y3		NPY	[Pro <sup>34</sup> ] NPY	NPY <sub>13-36</sub> PP		PYY
Y4	PP	PYY [Leu <sup>31</sup> ,Pro <sup>34</sup> ] NPY	NPY NPY <sub>2-36</sub>	NPY <sub>13-36</sub>		
Y5		PYY NPY NPY <sub>2-36</sub> [Leu <sup>31</sup> ,Pro <sup>34</sup> ] NPY		NPY <sub>13-36</sub>		

### NPY Receptor Pharmacology

NPY receptor pharmacology has historically been based on structure/activity relationships within the pancreatic polypeptide family. The entire family includes the namesake pancreatic polypeptide (PP), synthesized primarily by endocrine cells in the pancreas; peptide YY (PYY), synthesized primarily by endocrine cells in the gut; and NPY, synthesized primarily in neurons (Michel, M.C. (1991). Receptors for neuropeptide Y: multiple subtypes and multiple second messengers. Trends Pharmacol. 12: 389-394; Dumont et al., 1992; Wahlestedt and Reis, 1993). All pancreatic polypeptide family members share a compact structure involving a "PP-fold" and a conserved C-terminal hexapeptide ending in Tyr<sup>36</sup> (or Y<sup>36</sup> in the single letter code). The striking conservation of Y<sup>36</sup> has prompted the reference to the pancreatic polypeptides' receptors as "Y-type" receptors (Wahlestedt, C., L. Edvinsson, E. Ekblad, and R. Hakanson. Effects of neuropeptide Y at sympathetic neuroeffector junctions: Existence of Y<sub>1</sub> and Y<sub>2</sub> receptors. In: Neuronal messengers in vascular function, Fernstrom Symp. No 10., pp. 231-242. Eds A. Nobin and C.H. Owman. Elsevier: Amsterdam (1987)), all of which are proposed to function as seven transmembrane-spanning G protein-coupled receptors (Dumont et al., 1992).

The Y<sub>1</sub> receptor recognizes NPY = PYY >> PP (Grundemar et al., 1992). The receptor requires both the N- and the C-terminal regions of the peptides for optimal recognition. Exchange of Gln<sup>34</sup> in NPY or PYY with the analogous residue from PP (Pro<sup>34</sup>), however, is well-tolerated. The Y<sub>1</sub> receptor has been cloned from a variety of species including human, rat and mouse (Larhammar, D., A.G. Blomqvist, F. Yee, E. Jazin, H. Yoo, and C. Wahlestedt. (1992). Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y<sub>1</sub> type. J. Biol. Chem. 267: 10935-10938; Herzog, H., Y.J. Hort, H.J. Ball, G. Hayes, J. Shine, and L. Selbie. (1992). Cloned human neuropeptide Y receptor couples to two different second messenger systems. Proc. Natl. Acad. Sci. USA 89, 5794-5798; Eva, C., Oberto, A., Sprengel, R. and E. Genazzani. (1992). The murine NPY-1 receptor gene: structure and delineation of tissue specific expression. FEBS Lett. 314: 285-288; Eva, C., Keinänen, K., Monyer, H., Seeburg, P., and Sprengel, R. (1990). Molecular cloning of a novel G protein-coupled receptor that may belong to the neuropeptide receptor family. FEBS Lett. 271, 80-84). The Y<sub>2</sub> receptor recognizes PYY ~ NPY >> PP and is relatively tolerant of N-terminal deletion (Grundemar, L. and R. Hakanson (1994). Neuropeptide Y effector systems:

perspectives for drug development. Trends. Pharmacol. 15:153-159). The receptor has a strict requirement for structure in the C-terminus (Arg<sup>33</sup>-Gln<sup>34</sup>-Arg<sup>35</sup>-Tyr<sup>36</sup>-NH<sub>2</sub>); exchange of Gln<sup>34</sup> with Pro<sup>34</sup>, as in PP, is not well tolerated. The Y2 receptor has recently been cloned. The Y3 receptor is characterized by a strong preference for NPY over PYY and PP (Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082). [Pro<sup>34</sup>]NPY is reasonably well tolerated even though PP, which also contains Pro<sup>34</sup>, does not bind well to the Y3 receptor. This receptor (Y3) has not yet been cloned. The Y4 receptor binds PP > PYY > NPY. Like the Y1, the Y4 requires both the N- and the C-terminal regions of the peptides for optimal recognition. The "atypical Y1" or "feeding" receptor is defined exclusively by injection of several pancreatic polypeptide analogs into the paraventricular nucleus of the rat hypothalamus which stimulates feeding behavior with the following rank order: NPY<sub>2-36</sub> ≥ NPY ~ PYY ~ [Leu<sup>31</sup>,Pro<sup>34</sup>]NPY > NPY<sub>13-36</sub> (Kalra, S.P., Dube, M.G., Fournier, A., and Kalra, P.S. (1991). Structure-function analysis of stimulation of food intake by neuropeptide Y: Effects of receptor agonists. Physiology & Behavior 50: 5-9; Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y<sub>1</sub> receptor mediating this peptide's effect. Peptides 13: 581-587). The profile is similar to that of a Y1-like receptor except for the anomalous ability of NPY<sub>2-36</sub> to stimulate food intake with potency equivalent or better than that of NPY. A subsequent report by Balasubramaniam, A., Sherif, S., Johnson, M.E., Prabhakaran, M., Huang, Y., Fischer, J.E., and Chance, W.T. (1994). [D-Trp<sup>32</sup>]Neuropeptide Y: A competitive antagonist of NPY in rat hypothalamus. J. Med. Chem. 37: 311-815 showed that feeding can be regulated by [D-Trp<sup>32</sup>]NPY. While this peptide is presented as an NPY antagonist, the published data at least in part support a stimulatory effect of [D-Trp<sup>32</sup>]NPY on feeding. [D-Trp<sup>32</sup>]NPY thereby represents another diagnostic tool for receptor identification.

This plasmid (pcEXV-hY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Accession No. 75943.

The plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the rat Y5 receptor as to permit expression thereof has been designated as pcEXV-rY5 (ATCC Accession No. 75944).

This plasmid (pcEXV-rY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Accession No. CRL 75944.

A method for determining whether a ligand can specifically bind to a Y5 receptor comprises contacting a cell transfected with and expressing DNA encoding the Y5 receptor with the ligand under conditions permitting binding of ligands to such receptor, detecting the presence of any such ligand specifically bound to the Y5 receptor, and thereby determining whether the ligand specifically binds to the Y5 receptor.

A method for determining whether a ligand is a Y5 receptor antagonist comprises contacting a cell transfected with and expressing DNA encoding a Y5 receptor with the ligand in the presence of a known Y5 receptor agonist, such as PYY or NPY, under conditions permitting the activation of a functional Y5 receptor response, detecting a decrease in Y5 receptor activity, and thereby determining whether the ligand is a Y5 receptor antagonist.

In an embodiment of the above-described methods, the cell is non-neuronal in origin. In a further embodiment, the non-neuronal cell is a COS-7 cell, 293 human embryonic kidney cell, NIH-3T3 cell or L-M(TK-) cell.

The cell lines are transfected with a vector which is adapted for expression in a mammalian cell which comprises the regulatory elements necessary for expression of the DNA in the mammalian cell operatively linked to the DNA encoding the mammalian Y5 receptor as to permit expression thereof.

For example, such plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the human



Y5 receptor as to permit expression thereof designated pcEXV-hY5 (ATCC Accession No. 75943).

### Experimental Details

## MATERIALS AND METHODS

### cDNA Cloning

Total RNA was prepared by a modification of the guanidine thiocyanate method (Kingston, 1987), from 5 grams of rat hypothalamus (Rockland, Gilbertsville, PA). Poly A<sup>+</sup>RNA was purified with a FastTrack kit (Invitrogen Corp., San Diego, CA). Double stranded (ds) cDNA was synthesized from 7 mg of poly A<sup>+</sup> RNA according to Gubler and Hoffman (Gubler, U and B.J. Hoffman. (1983). A simple and very efficient method for generating cDNA libraries. Gene. 25, 263-269), except that ligase was omitted in the second strand cDNA synthesis. The resulting DS cDNA was ligated to BstXI/EcoRI adaptors (Invitrogen Corp.), the excess of adaptors was removed by chromatography on Sephacryl 500 HR (Pharmacia®-LKB) and the ds-cDNA size selected on a Gen-Pak Fax HPLC column (Millipore Corp., Milford, MA). High molecular weight fractions were ligated in pEXJ.BS (A cDNA cloning expression vector derived from pcEXV-3; Okayama, H. and P. Berg (1983). A cDNA cloning vector that permits expression of cDNA inserts in mammalian cells. Mol. Cell. Biol. 3: 280-289; Miller, J. and Germain, R.N. (1986). Efficient cell surface expression of class II MHC molecules in the absence of associated invariant chain. J. Exp. Med. 164: 1478-1489) cut by BstXI as described by Aruffo and Seed (Aruffo, A. and Seed, B. (1987). Molecular cloning of a CD28 cDNA by a high efficiency COS cell expression system. PNAS, 84, 8573-8577). The ligated DNA was electroporated in E.Coli MC 1061 F<sup>+</sup> (Gene Pulser, Biorad). A total of  $3.4 \times 10^6$  independent clones with an insert mean size of 2.7 kb could be generated. The library was plated on Petri dishes (Ampicillin selection) in pools of  $6.9$  to  $8.2 \times 10^3$  independent clones. After 18 hours amplification, the bacteria from each pool were scraped, resuspended in 4 ml of LB media and 1.5 ml processed for plasmid purification with a QIAprep-8 plasmid kit (Qiagen Inc, Chatsworth, CA). 1 ml aliquots of each bacterial pool were stored at -85°C in 20% glycerol.

Isolation of a cDNA clone encoding an atypical rat hypothalamic NPY5 receptor

DNA from pools of » 7500 independent clones was transfected into COS-7 cells by a modification of the DEAE-dextran procedure (Warden, D. and H.V. Thorne. (1968). Infectivity of polyoma virus DNA for mouse embryo cells in presence of diethylaminoethyl-dextran. J. Gen. Virol. 3, 371). COS-7 cells were grown in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal calf serum, 100 U/ml of penicillin, 100 mg/ml of streptomycin, 2 mM L-glutamine (DMEM-C) at 37°C in 5% CO<sub>2</sub>. The cells were seeded one day before transfection at a density of 30,000 cells/cm<sup>2</sup> on Lab-Tek chamber slides (1 chamber, Permanox slide from Nunc Inc., Naperville, IL). On the next day, cells were washed twice with PBS, 735 µl of transfection cocktail was added containing 1/10 of the DNA from each pool and DEAE-dextran (500 mg/ml) in Opti-MEM I serum free media (Gibco®BRL LifeTechnologies Inc. Grand Island, NY). After a 30 min. incubation at 37°C, 3 µl of chloroquine (80 mM in DMEM-C) was added and the cells incubated a further 2.5 hours at 37°C. The media was aspirated from each chamber and 2 µl of 10% DMSO in DMEM-C added. After 2.5 min. incubation at room temperature, the media was aspirated, each chamber washed once with 2 ml PBS, the cells incubated 48 hours in DMEM-C and the binding assay was performed on the slides. After one wash with PBS, positive pools were identified by incubating the cells with 1 nM (3x10<sup>6</sup> cpm per slide) of porcine [<sup>125</sup>I]-PYY (NEN; SA=2200 Ci/mmol) in 20 mM Hepes-NaOH pH 7.4, CaCl<sub>2</sub> 1.26 mM, MgSO<sub>4</sub> 0.81 mM, KH<sub>2</sub>PO<sub>4</sub> 0.44 mM, KCL 5.4, NaCl 10 mM, .1% BSA, 0.1% bacitracin for 1 hour at room temperature. After six washes (three seconds each) in binding buffer without ligand, the monolayers were fixed in 2.5% glutaraldehyde in PBS for five minutes, washed twice for two minutes in PBS, dehydrated in ethanol baths for two minutes each (70, 80, 95, 100%) and air dried. The slides were then dipped in 100% photoemulsion (Kodak® type NTB2) at 42°C and exposed in the dark for 48 hours at 4°C in light proof boxes containing drierite. Slides were developed for three minutes in Kodak® D19 developer (32 g/l of water), rinsed in water, fixed in Kodak® fixer for 5 minutes, rinsed in water, air dried and mounted with Aqua-Mount (Lerner Laboratories, Pittsburgh, PA). Slides were screened at 25x total magnification. A single clone, CG-18, was isolated by SIB selection as described (McCormick, 1987). DS-DNA was sequenced with a Sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer. Nucleotide and peptide sequence analysis were performed with GCG programs (Genetics Computer group, Madison, WI).

### Isolation of the human Y5 homolog

Using rat oligonucleotide primers in TM 3 (sense primer; position 484-509 in SEQ ID NO:1) and in TM 6 (antisense primer; position 1219-1243 in SEQ ID NO: 1), a human hippocampal cDNA library has been screened using the polymerase chain reaction. 1  $\mu$ l ( $4 \times 10^6$  bacteria) of each of 450 amplified pools containing each »5000 independent clones and representing a total of  $2.2 \times 10^6$  was subjected directly to 40 cycles of PCR and the resulting products analyzed by agarose gel electrophoresis. One of three positive pools was analyzed further and by sib selection a single cDNA clone was isolated and characterized. This cDNA turned out to be full length and in the correct orientation for expression. DS-DNA was sequenced with a sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer.

### Cell Culture

COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37°C, 5% CO<sub>2</sub>. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO<sub>2</sub>. Stock plates of 293 cells were trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LMT(k)- cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO<sub>2</sub>. Stock plates of COS-7 cells were trypsinized and split 1:10 every 3-4 days.

### Stable Transfection

Human Y5 and rat Y5 receptors were co-transfected with a G-418 resistant gene into mouse fibroblast LMT(k)- cells by a calcium phosphate transfection method (Cullen, B.

(1987). Use of eukaryotic expression technology in the functional analysis of cloned genes. Methods Enzymol. 152: 685-704). Stably transfected cells were selected with G-418.

## EXPERIMENTAL RESULTS

### cDNA Cloning

In order to clone a rat hypothalamic "atypical" NPY receptor subtype, applicants used an expression cloning strategy in COS-7 cells (Gearing et al, 1989; Kluxen, F.W., Bruns, C. and Lubbert H. (1992). Expression cloning of a rat brain somatostatin receptor cDNA. Proc. Natl. Acad. Sci. USA 89, 4618-4622; Kieffer, B., Befort, K., Gaveriaux-Ruff, C. and Hirth, C.G. (1992). The

$\delta$ -opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. Proc. natl. Acad. Sci. USA 89, 12048-12052). This strategy was chosen for its extreme sensitivity since it allows detection of a single "receptor positive" cell by direct microscopic autoradiography. Since the "atypical" receptor has only been described in feeding behavior studies involving injection of NPY and NPY related ligands in rat hypothalamus (see introduction), applicants first examined its binding profile by running competitive displacement studies of  $^{125}\text{I}$ -PYY and  $^{125}\text{I}$ -PYY<sub>3-36</sub> on membranes prepared from rat hypothalamus. The competitive displacement data indicate: 1) Human PP is able to displace 20% of the bound  $^{125}\text{I}$ -PYY with an  $\text{IC}_{50}$  of 11 nM (Fig. 1 and Table 2). As can be seen in table 5, this value does not fit with the isolated rat Y1, Y2 and Y4 clones and could therefore correspond to another NPY/PYY receptor subtype. 2) [Leu<sub>31</sub>, Pro<sub>34</sub>] NPY (a Y1 specific ligand) is able to displace with high affinity ( $\text{IC}_{50}$  of 0.38) 27% of the bound  $^{125}\text{I}$ -PYY<sub>3-36</sub> ligand (a Y2 specific ligand) (Fig. 2 and table 2). These data provide the first evidence based on a binding assay that rat hypothalamic membranes could carry an NPY receptor subtype with a mixed Y1/Y2 pharmacology (referred to as the "atypical" subtype) which fits with the pharmacology defined in feeding behavior studies.

TABLE 2: Pharmacological profile of the rat hypothalamus.

Binding data reflect competitive displacement of  $^{125}\text{I}$ -PYY and  $^{125}\text{I}$ -PYY<sub>3-36</sub> from rat hypothalamic membranes. Peptides were tested at concentrations ranging from 0.001 nM to 100 nM unless noted. The  $\text{IC}_{50}$  value corresponding to 50% displacement, and the

percentage of displacement relative to that produced by 300 nM human NPY, were determined by nonlinear regression analysis. Data shown are representative of at least two independent experiments.

TABLE 2

Peptide	IC <sub>50</sub> Values, nM (% NPY-produced displacement)	
	<sup>125</sup> I-PYY	<sup>125</sup> I-PYY <sub>3-36</sub>
human NPY	0.82 (100%)	1.5 (100%)
human NPY <sub>2-36</sub>	2.3 (100%)	1.2 (100%)
human [Leu <sup>31</sup> ,Pro <sup>34</sup> ]NPY	0.21 (44%) 340 (56%)	0.38 (27%) 250 (73%)
human PYY	1.3 (100%)	0.29 (100%)
human PP	11 (20%)	untested

Based on the above data, a rat hypothalamic cDNA library of  $3 \times 10^6$  independent recombinants with a 2.7 kb average insert size was fractionated into 450 pools of ~7500 independent clones. All pools were tested in a binding assay with <sup>125</sup>I-PYY as described (Y2 patent). Seven pools gave rise to positive cells in the screening assay (# 81, 92, 147, 246, 254, 290, 312). Since Y1, Y2, Y4 and Y5 receptor subtypes (by PCR or binding analysis) are expressed in rat hypothalamus, applicants analyzed the DNA of positive pools by PCR with rat Y1, Y2 and Y4 specific primers. Pools # 147, 246, 254 and 312 turned out to contain cDNAs encoding a Y1 receptor, pool # 290 turned out to encode a Y2 subtype, but pools # 81 and 92 were negative by PCR analysis for Y1, Y2 and Y4 and therefore likely contained a cDNA encoding a new rat hypothalamic NPY receptor (Y5). Pools # 81 and 92 later turned out to contain an identical NPY receptor cDNA. Pool 92 was subjected to sib selection as described until a single clone was isolated (designated CG-18).

The isolated clone carries a 2.8 kb cDNA. This cDNA contains an open reading frame between nucleotides 779 and 2146 that encodes a 456 amino acid protein. The long 5' untranslated region could be involved in the regulation of translation efficiency or mRNA stability. The flanking sequence around the putative initiation codon does not conform to the Kozak consensus sequence for optimal translation initiation (Kozak, M. (1989). The scanning model for translation: an update. J. Cell Biol. 108, 229-241; Kozak, M. (1991). Structural features in eukaryotic mRNAs that modulate the initiation of translation. J. Biol. Chem. 266, 19867-19870). The hydrophobicity plot displayed seven hydrophobic, putative membrane spanning regions which makes the rat hypothalamic Y5 receptor a member of the G-protein coupled superfamily. The nucleotide and deduced amino acid sequences are shown in SEQ ID NOS: 1 and 2, respectively.

Localization studies show that the Y5 mRNA is present in several areas of the rat hippocampus. Assuming a comparable localization in human brain, applicants screened a human hippocampal cDNA library with rat oligonucleotide primers which were shown to yield a DNA band of the expected size in a PCR reaction run on human hippocampal cDNA. Using this PCR screening strategy (Gerald et al, 1994, submitted for publication), three positive pools were identified. One of these pools was analyzed further, and an isolated clone was purified by sib selection. The isolated clone (CG-19) turned out to contain a full length cDNA cloned in the correct orientation for functional expression (see below). The human Y5 nucleotide and deduced amino acid sequences are shown in SEQ ID NOS 3 and 4, respectively. When compared to the rat Y5 receptor the human sequence shows 84.1% nucleotide identity and 87.2% amino acid identity. The rat protein sequence is one amino acid longer at the very end of both amino and carboxy tails of the receptor when compared to the rat. Both pharmacological profiles and functional characteristics of the rat and human Y5 receptor subtype homologs may be expected to match closely.

When the human and rat Y5 receptor sequences were compared to other NPY receptor subtypes or to other human G protein-coupled receptor subtypes, both overall and transmembrane domain identities are very low, showing that the Y5 receptor genes are not closely related to any other previously characterized cDNAs.

The compounds according to the present invention and their pharmaceutically acceptable salts have proven to exhibit pronounced and selective affinity to the Y5 receptor subtype

(shown in Y5 binding test) and in vitro and in vivo antagonistic properties. These properties are shown in vitro by their ability to inhibit NPY-induced calcium increase in stable transfected cells expressing the Y5 receptor and in vivo by their ability to inhibit food intake induced by intracerebroventricular application of NPY or 24 h food deprivation in conscious rats.

#### Binding experiments

The selective affinity of the compounds according to the present invention to the Y5 receptor is detected in a Y5 binding assay using LM(tk-)-h-NPY5-7 cells which stably express the human NPY Y5 receptor or HEK-293 cells stably expressing the rat NPY Y5 receptor.

The following buffers are used for the preparation of membranes and for binding assay:

a) buffer 1 (homogenisation buffer, pH 7.7 at 4°C) contains Tris-HCl [FLUKA, Buchs, Switzerland] (20 mM) and ethylenediamine tetraacetate (EDTA) [FLUKA, Buchs, Switzerland] (5 mM); b) buffer 2 (suspension buffer, pH: 7.4 at room temperature) contains N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) [Boehringer Mannheim, Germany] (20 mM), NaCl (10 mM), CaCl<sub>2</sub> (1.26 mM), MgSO<sub>4</sub> (0.81 mM) and KH<sub>2</sub>PO<sub>4</sub> (0.22 mM); buffer 3 (binding buffer, pH 7.4 at room temperature) contains HEPES (20 mM), NaCl (10 mM), CaCl<sub>2</sub> (1.26 mM), MgSO<sub>4</sub> (0.81 mM), KH<sub>2</sub>PO<sub>4</sub> (0.22 mM) and 1 mg/ml bovine serum albumin [FLUKA].

Cells are washed in phosphate buffered saline and harvested using a rubber policeman. The cells are homogenised using a Polytron homogeniser (3 bursts of 8 seconds) in ice-cold hypotonic buffer (buffer 1, pH 7.7 at 4°C). The homogenate is centrifuged at 32,000 x g for 20 min at 4°C. The pellets are resuspended in the same buffer and recentrifuged. The final pellets are suspended in buffer 2. Protein concentration is measured by the method of Bradford using the Pierce reagent [PIERCE, Rockford, USA], with bovine serum albumin as standard. The crude membrane preparation is aliquoted, flash-frozen in liquid nitrogen and stored at -80°C. Before use, 0.1% (1 mg/ml) bovine serum albumin is added.

<sup>125</sup>I-[Pro<sup>34</sup>]hPYY (60 pM, Anawa, Wangen, Switzerland) dissolved in buffer 3 is used as radioligand. All test compounds are dissolved in dimethyl sulfoxide (DMSO) at 10<sup>-2</sup> M and diluted to 10<sup>-3</sup> M in buffer 3. Subsequent dilutions are in buffer 3 plus 10% DMSO. Incubations are performed in Millipore Multiscreen FC filter plates [Millipore, Bedford, USA]. The filters in each well are pretreated with 2% polyethyleneimine for 30 min and rinsed once with 300 microL buffer 3 before use. The following are pipetted into each well: 20 microL

buffer 3, 25 microL  $^{125}\text{I}$ -[Pro $^{34}$ ]hPYY [SAXON, Hannover, Germany] (600 pM); 25 microL test compound (or binding buffer for the controls); 180 microL crude membrane suspension (approximately 5 microg protein). Incubations are performed at room temperature for 2h. Non-specific binding is defined as the binding remaining in the presence of 1 microM [Pro $^{34}$ ]hPYY. The incubations are terminated by rapid filtration and washing four times with 300microL phosphate buffered saline. The filters are removed from the wells, placed into plastic tubes and assayed for radioactivity in a gamma counter [Gammamaster, WALLAC, Finland].

The IC<sub>50</sub> values of the compounds according to this invention at the human Y5 receptor range especially between about 0.1 nM and about 10 microM. Representatives are, for example, the final products of working examples 30, 71 and 128, for which following IC<sub>50</sub> values [ $\mu\text{M/L}$ ] were determined: 0.01 (Ex. 30); 0.049 (Ex. 71); 0.05 (Ex. 128).

#### Measurements of calcium transient

For the determination of in vitro antagonistic properties of the compounds according to the present invention, stably transfected LM(tk-)-hY5-7 cells are used in which a NPY-induced calcium transient is measured as described below. Cells are harvested in a medium containing EDTA (0.5 mM) and phosphate buffered saline (PBS). Cells are then washed in phosphate buffered saline solution and loaded for 90 min at room temperature and pH 7.4 with 10 microM FLUO-AM (fluoro-3-acetoxy methylester, supplemented with pluronic acid as suggested by the manufacturer, Molecular Probes Inc., Eugene, Oregon, USA) in a cell culture buffer of the following composition (NaCl 120 mM, MgCl<sub>2</sub> 1 mM, KCl 5.4 mM, NaH<sub>2</sub>PO<sub>4</sub> 0.33 mM, glucose 11 mM, taurine 5 mM, pyruvate 2 mM, glutamine 1.5 mM HEPES 10 mM, insulin 10 U/l, BSA 0.1% at for 90 min at room temperature. After centrifugation the cells are resuspended in the cell culture buffer at a concentration of 3-4 million cells/ml and supplemented with 200 microM sulfinpyrazone.

Calcium transients are measured at room temperature in a milliliter plate using a Cytofluor 2350 (Millipore) with wavelength settings at 485 nm for excitation and 530 nm for emission. 180 microL of cells suspension are preincubated in the presence of various amounts of compounds dissolved in 2 microL DMSO in triplicates ( or 2 microL DMSO for the controls) for 5 min and then NPY is added at a final concentration of 100 nM. The compound concentrations giving 50% inhibition of the maximum of the Ca transients are then calculated.



In this cell system, NPY induces Ca transients with an EC<sub>50</sub> of 50 nM. The data are analyzed using a Microsoft Excel software. The concentrations which cause a 50% inhibition of the initial control values are given as IC<sub>50</sub> values. The IC<sub>50</sub> values are determined for the compounds according to the present invention and their pharmaceutically acceptable salts.

The property of the compounds according to the present invention and their pharmaceutically acceptable salts to inhibit NPY-induced increase intracellular calcium indicates their antagonistic properties with IC<sub>50</sub> values ranging especially between about 0.1 nM and about 10 µM.

#### Measurements of NPY-induced food intake in conscious rats

In addition this antagonistic property of the Y<sub>5</sub> receptor subtype is also observed in-vivo in conscious rats by their ability to inhibit NPY-induced food intake. For these determinations food intake is measured in normal satiated rats after intracerebroventricular application (i.c.v.) of neuropeptide Y [BACHEM, Feinchemikalien, Bubendorf, Switzerland] in the presence or absence of the compounds according to the present invention. Male Sprague-Dawley rats weighing 180-220 g are used for all experiments. They are individually housed in stainless steel cages and maintained on a 11:13 h light-dark schedule (lights off at 1800 h) under controlled temperature (21-23 °C) at all times. Water and food (NAFAG lab chow pellets) [NAFAG, Gossau, Switzerland] are available ad libitum.

Under pentobarbital [ VETERINARIA AB, Zürich, Switzerland] anesthesia, all rats are implanted with a stainless steel guide cannula targeted at the right lateral ventricle. Stereotaxic coordinates, with the incisor bar set -2.0 mm below interaural line, are : -0.8 mm anterior and +1.3 mm lateral to bregma. The guide cannula is placed on the dura. Injection cannulas extended the guide cannulas -3.8 mm ventrally to the skull surface. Animals are allowed at least 4 days of recovery postoperatively before being used in the experiments.

Cannula placement is checked postoperatively by testing all rats for their drinking response to a 50 ng intracerebroventricular (icv) injection of angiotensin II . Only rats which drink at least 2.5 ml of water within 30 min after angiotensin II injection are used in the feeding studies. Injections are made in the morning 2 hours after light onset. Peptides are injected in artificial cerebrospinal fluid (ACSF) [FLUKA, Buchs, Switzerland] in a volume of 5 µl. The ACSF contains NaCl 124 mM, KCl 3.75 mM, CaCl<sub>2</sub> 2.5 mM, MgSO<sub>4</sub> 2.0 mM, KH<sub>2</sub>PO<sub>4</sub> 0.22 mM, NaHCO<sub>3</sub> 26 mM and glucose 10 mM. NPY (300 pmole) is administered by the

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intracerebroventricular route 10-60 minutes after administration of compounds or vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v) [SIGMA, Buchs, Switzerland].

Food intake is measured by placing preweighed pellets into the cages at the time of NPY injection. Pellets are removed from the cage subsequently at each time point indicated in the figures and replaced with a new set of preweighed pellets.

All results are presented as means  $\pm$  SEM. Statistical analysis is performed by analysis of variance using Student-Newman-Keuls test.

The compounds according to the present invention inhibit NPY-induced food intake in rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

#### Measurements of food intake in 24 hours food deprived rats

Based on the observation that food deprivation induces an increase in the hypothalamic NPY levels, it is assumed that NPY mediates food intake induced by food deprivation. Thus, the compounds according to the present invention are also tested in rats after 24 hours food deprivation. These experiments are conducted with male Sprague-Dawley (CIBA-GEIGY AG, Sisseln, Switzerland) rats weighing between 220 and 250 g. The animals are housed in individual cages for the duration of the study and allowed free access to normal food together with tap water. The animals are maintained in room with a 12 h light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the individual cages the rats undergo a 2-4 days equilibration period, during which they are habituated to their new environment and to eating a powdered or pellet diet [NAFAG, Gossau, Switzerland]. At the end of the equilibration period, food is removed from the animals for 24 hours starting at 8.00 a.m. At the end of the fasting period the animals are injected intraperitoneally, intravenously or orally either with the compounds according to the present invention or an equivalent volume of vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v) and 10-60 min later the food is returned to them. Food intake at various time periods is monitored over the following 24 hour period. Inhibition of food intake by the compounds according to the present invention is given in percentage of the respective control vehicle-treated rats.

The compounds according to the present invention inhibit food intake in this food deprived rat model in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration. Representative is, for example, the final

product of working example 128, for which an inhibition of food intake of 62% versus the respective control vehicle-treated animals after i.p. application of 30 mg/kg was determined.

#### Measurements of food intake in obese Zucker rats

The antiobesity efficacy of the compounds according to the present invention can also be shown in Zucker obese rats, an art-known animal model of obesity. These studies are conducted with male Zucker fatty rats (fa/fa) [HARLAN CPB, Austerlitz, NL] weighing between 480 and 500 g. Animals are individually housed in metabolism cages for the duration of the study and allowed free access to powdered food together with tap water. The animals are maintained in a room with a 12 hour light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the metabolism cages the rats undergo a 6 day equilibration period, during which they are habituated to their new environment and to eating a powdered diet. At the end of the equilibration period, food intake during the light and dark phases is determined. After a 3 day control period, the animals are treated with the compounds according to the present invention or vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v).

The compounds according to the present invention inhibit food intake in Zucker obese rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

The above experiments clearly demonstrate that the Y5 receptor subtype is the primary mediator of NPY-induced feeding and that corresponding antagonists can be used for the treatment of obesity and related disorders [*Nature*, Vol. 382, 168-171 (1996)].

The compounds according to the present invention can inhibit food intake induced either by intracerebroventricular application of NPY or by food deprivation or as well as spontaneous eating in the Zucker obese rat. Thus, the compounds according to the present invention can especially be used for the treatment and prophylaxis of disorders or diseases associated with the Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain and additionally in the treatment of sexual/reproductive

disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The compounds according to the present invention act as antagonists of neuropeptide Y (NPY) binding at the Y5 receptor subtype. By virtue of their Y5 receptor antagonistic property, the compounds of the formula (I) and their pharmaceutically acceptable salts can therefore be used, for example, as pharmaceutical active ingredients in pharmaceutical compositions which are employed, for example, for the prophylaxis and treatment of diseases and disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the manufacture of a pharmaceutical composition for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and

additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R<sub>2</sub> represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) hydroxy, lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cyclo-alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is disubstituted by lower alkylene {which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>} or which is disubstituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X<sub>1</sub>(X<sub>2</sub>)(X<sub>3</sub>) wherein, (a) if X<sub>1</sub> is -CH-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>r</sub>-, or -(CH<sub>2</sub>)<sub>s</sub>-X<sub>4</sub>-CO-(CH<sub>2</sub>)<sub>t</sub>-; or, (b) if X<sub>1</sub> is -N-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -CO-(CH<sub>2</sub>)<sub>u</sub>-; [X<sub>4</sub> being -CH<sub>2</sub>-, -N(R<sub>1</sub>)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X<sub>4</sub> is different from -CH<sub>2</sub>-];

$R_3$  and  $R_4$ , independently of one another, represent

- (i) hydrogen, lower alkyl, lower alkenyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and  $-S(O)_n-R$ ;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ , or  $NR_0$ ] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

- (i) halogen, lower alkyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3$ - $C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iv) amino, substituted amino;
- (v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl,

pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinoliny, isoquinoliny, or quinazoliny;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R<sub>2</sub> represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxycarbonyl, or by substituted carbamoyl;

(ii) substituted amino;

(iii) lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cyclo-alkoxy, or (carbocyclic or heterocyclic) aryl-lower alkoxy,;

(iv) hydroxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined

above, or the group  $-N(R)(R_1)$  represents amino which is di-substituted by lower alkylene {which may be interrupted by O or  $NR_0$ } or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring}; or

(vii) an element of formula  $-X_1(X_2)(X_3)$  wherein, (a) if  $X_1$  is  $-CH-$ ,  $X_2$  together with  $X_3$  represent a structural element of formula  $-X_4-(CO)_p-(CH_2)_o-$ ,  $-(CH_2)_q-X_4-(CO)_p-(CH_2)_r-$ , or  $-(CH_2)_s-X_4-CO-(CH_2)_t-$ ; or, (b) if  $X_1$  is  $-N-$ ,  $X_2$  together with  $X_3$  represent a structural element of formula  $-CO-(CH_2)_u-$ ; [ $X_4$  being  $-CH_2-$ ,  $-N(R_1)-$  or  $-O-$ ; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0,  $X_4$  is different from  $-CH_2-$ ];

$R_3$  and  $R_4$ , independently of one another, represent

- (i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and substituted carbamoyl;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ , or  $NR_0$ ];

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene which, in each case, is unsubstituted or substituted by halogen, cyano, lower alkyl, halo-lower alkyl, lower alkoxy, lower alkanoyloxy, or lower alkanoyl;

wherein, in each case, if not indicated otherwise, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

- (i) halogen, lower alkyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3-C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy,



amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) substituted amino;

(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, is derived from phenyl, naphthyl or pyridyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk<sub>1</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl or lower alkyl which is substituted by lower alkoxy-carbonyl;

R<sub>2</sub> represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, or phenyl;

- (ii) amino, amino which is mono-substituted by lower alkyl, by lower alkoxy-lower alkyl, by phenyl, by pyridyl, or which is disubstituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene;
- (iii) hydroxy, lower alkanoyloxy, or lower alkoxy which is unsubstituted or substituted by hydroxy, by lower alkoxy, by phenyl-lower alkoxy, by lower-alkanoyloxy, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl or by phenyl;
- (iv) a group selected from -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R being lower alkyl, lower alkoxy-lower alkyl, phenyl, or naphthyl, and the group -N(R)(R<sub>1</sub>) represents amino which is mono-substituted by lower alkyl or by lower alkoxy-lower alkyl, or which is di-substituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene {which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or lower alkyl}];
- (vi) carbamoyl;

R<sub>3</sub> represents hydrogen, lower alkyl which is unsubstituted or substituted by C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, by phenyl, or by di-lower alkylamino, or represents C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, hydroxy, and carbamoyl, or represents indazolyl;

R<sub>4</sub> represents hydrogen or lower alkyl which is unsubstituted or substituted by lower alkoxy-carbonyl; or

R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, or oxy-lower alkylene-oxy, or represents naphthylene;

wherein the benzo ring A is unsubstituted or substituted a substituent selected from the group consisting of: halogen, nitro, amino, di-lower alkylamino, lower alkyl, lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkyl, di-(lower alkyl)-amino-lower alkyl, phenyl, and lower alkanoyl.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk<sub>1</sub> represents a single bond;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen or lower alkyl;

R<sub>2</sub> represents

- (i) hydrogen, halogen, cyano, nitro, lower alkyl, or phenyl;
- (ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene;
- (iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl or by phenyl;
- (iv) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene (which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or lower alkyl)];

R<sub>3</sub> represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R<sub>4</sub> represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, lower alkoxy-lower alkyl;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, halo-lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

- (a) alk<sub>1</sub> and alk<sub>2</sub> both represents a single bond; and

R<sub>2</sub> represents (i) hydrogen, halogen, cyano, nitro, lower alkyl, or phenyl;  
(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene;  
(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, or by phenyl; or

(b)  $\text{alk}_1$  represents a single bond; and

$\text{alk}_2$  represents a single bond or  $\text{C}_1\text{-C}_3$ -alkylene; and, in each case,

$\text{R}_2$  represents (iv) a group selected from  $-\text{NR}_1\text{-CO-R}$ ,  $-\text{NR}_1\text{-SO}_2\text{-R}$ ,  $-\text{NR}_1\text{-SO}_2\text{-NR}_1\text{-R}$ ,  $-\text{SO}_2\text{-R}$ , or  $-\text{SO}_2\text{-NR}_1\text{-R}$ , [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl,  $\text{R}_1$  being as defined below, or the group  $-\text{N(R)}(\text{R}_1)$  represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by  $\text{C}_2\text{-C}_6$ -alkylene {which may be interrupted by O or  $\text{NR}_0$ ,  $\text{R}_0$  being hydrogen or lower alkyl}];

$\text{R}_1$  represents hydrogen or lower alkyl;

$\text{R}_3$  represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

$\text{R}_4$  represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, halo-lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a)  $\text{alk}_1$  and  $\text{alk}_2$  both represents a single bond; and

$\text{R}_2$  represents hydrogen, amino which is disubstituted by  $\text{C}_2\text{-C}_6$ -alkylene, especially pentylene, or  $\text{C}_1\text{-C}_4$ -alkoxy, especially methoxy; or

(b)  $\text{alk}_1$  represents a single bond;  $\text{alk}_2$  represents  $\text{C}_1\text{-C}_3$ -alkylene; and

$\text{R}_2$  represents (iv) a group selected from  $-\text{NH-SO}_2\text{-R}$ ,  $-\text{SO}_2\text{-R}$ , or  $-\text{SO}_2\text{-NH-R}$ , [R being  $\text{C}_1\text{-C}_4$ -alkyl, or naphthyl, or the group  $-\text{NH(R)}$  represents amino which is mono-substituted by  $\text{C}_1\text{-C}_4$ -alkyl, by hydroxy- $\text{C}_1\text{-C}_4$ -alkyl, or by naphthyl, or which is di-substituted by  $\text{C}_1\text{-C}_4$ -alkyl or by  $\text{C}_2\text{-C}_6$ -alkylene {which may be interrupted by O or  $\text{NR}_0$ ,  $\text{R}_0$  being hydrogen or  $\text{C}_1\text{-C}_4$ -alkyl}];

and, in each case,

R<sub>1</sub> represents hydrogen;

R<sub>3</sub> represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, and oxy-C<sub>1</sub>-C<sub>4</sub>-alkylene-oxy; and

R<sub>4</sub> represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, or C<sub>1</sub>-C<sub>4</sub>-alkoxy;

wherein the benzo ring A is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk<sub>1</sub> represents a single bond;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>- or C<sub>2</sub>-alkylene;

R<sub>1</sub> represents hydrogen;

R<sub>2</sub> represents hydrogen, hydroxy, C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially methoxy, lower alkoxy-lower alkoxy, phenyl-lower alkoxy-lower alkoxy, amino, amino which is disubstituted by C<sub>2</sub>-C<sub>6</sub>-alkylene, especially pentylene, lower alkoxycarbonyl-amino, or -SO<sub>2</sub>-R or -SO<sub>2</sub>-NH-R and R being C<sub>1</sub>-C<sub>4</sub>-alkyl, especially methyl; and, in each case;

R<sub>3</sub> represents C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl-lower alkyl, or phenyl which is unsubstituted or is substituted by halogen, hydroxy, or lower alkoxy;

R<sub>4</sub> represents hydrogen; and

X represents 1,4-phenylene or 1,3-phenylene which is di-substituted by oxy-methylene-oxy;

wherein the benzo ring A is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

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(a)  $\text{alk}_1$  and  $\text{alk}_2$  both represent a single bond; and  $\text{R}_2$  represents hydrogen,  $\text{C}_1\text{-C}_4$ -alkoxy, especially methoxy, or amino which is disubstituted by  $\text{C}_2\text{-C}_6$ -alkylene, especially pentylene; or

(b)  $\text{alk}_1$  represents a single bond; and  $\text{alk}_2$  represents  $\text{C}_1$ - or  $\text{C}_2$ -alkylene; and  $\text{R}_2$  represents  $-\text{SO}_2\text{-R}$  or  $-\text{SO}_2\text{-NH-R}$  and  $\text{R}$  being  $\text{C}_1\text{-C}_4$ -alkyl, especially methyl; and, in each case,

$\text{R}_1$  represents hydrogen;

$\text{R}_3$  represents phenyl which is unsubstituted or is substituted by lower alkoxy;

$\text{R}_4$  represents hydrogen; and

$\text{X}$  represents 1,4-phenylene;

wherein the benzo ring A is unsubstituted or substituted by  $\text{C}_1\text{-C}_4$ -alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention most preferably relates to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a)  $\text{alk}_1$  and  $\text{alk}_2$  both represent a single bond; and  $\text{R}_2$  is hydrogen, 1-piperidino or  $\text{C}_1\text{-C}_4$ -alkoxy, especially methoxy; the benzo ring A is unsubstituted or substituted in position 8 of the quinazoline ring by  $\text{C}_1\text{-C}_4$ -alkoxy, especially methoxy, or

(b)  $\text{alk}_1$  is a single bond and  $\text{alk}_2$  represents methylene; and  $\text{R}_2$  is  $-\text{SO}_2\text{-NH-R}$  and  $\text{R}$  is  $\text{C}_1\text{-C}_4$ -alkyl, especially methyl; the benzo ring A is unsubstituted; and, in each case,  $\text{R}_1$  is hydrogen;  $\text{R}_3$  is phenyl;  $\text{R}_4$  is hydrogen;  $\text{X}$  is 1,4-phenylene.

The invention most preferably relates to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

$\text{alk}_1$  and  $\text{alk}_2$  both represent a single bond;

$\text{R}_1$  is hydrogen;

$\text{R}_4$  is hydrogen;

$\text{X}$  is 1,4-phenylene;

$\text{R}_2$  is  $\text{C}_1\text{-C}_4$ -alkoxy, especially methoxy, and  $\text{R}_3$  is phenyl which is substituted by hydroxy, especially 3-hydroxy-phenyl; or

$R_2$  is  $C_1$ - $C_4$ -alkoxy- $C_1$ - $C_4$ -alkoxy, especially 2-methoxy-ethoxy, or 1-piperidino; and  
 $R_3$  is phenyl; and  
 the benzo ring A is unsubstituted or substituted in position 8 of the quinazoline ring by  $C_1$ - $C_4$ -alkoxy, especially methoxy.

The invention likewise relates to a new compound of formula (I) or a salt thereof as described hereinbefore or hereinafter.

The invention relates especially to a new compound of formula (I) or a salt thereof, for example, in which

$alk_1$  and  $alk_2$ , independently of one another, represent a single bond or lower alkylene;

$R_1$  represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

$R_2$  represents a group selected from  $-CH(OH)-R$ ,  $-CO-R$ ,  $-NR_1-CO-O-R$ ,  $-NR_1-CO-R$ ,  $-NR_1-CO-NR_1-R$ ,  $-NR_1-SO_2-R$ ,  $-NR_1-SO_2-NR_1-R$ ,  $-SO_2-R$ ,  $-SO_2-NR_1-R$ , or  $-SO_2-NR_1-CO-R$ , [ $R$  being as defined below and  $R_1$  being as defined above, or the group  $-N(R)(R_1)$  represents amino which is di-substituted by lower alkylene {which may be interrupted by O,  $S(O)_n$  or  $NR_0$ } or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula  $-X_1(X_2)(X_3)$  wherein, (a) if  $X_1$  is  $-CH-$ ,  $X_2$  together with  $X_3$  represent a structural element of formula  $-X_4(CO)_p(CH_2)_o-$ ,  $-(CH_2)_q-X_4(CO)_p(CH_2)_r-$ , or  $-(CH_2)_s-X_4-CO-(CH_2)_t-$ ; or, (b) if  $X_1$  is  $-N-$ ,  $X_2$  together with  $X_3$  represent a structural element of formula  $-CO-(CH_2)_u-$ ; [ $X_4$  being  $-CH_2-$ ,  $-N(R_1)-$  or  $-O-$ ; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0,  $X_4$  is different from  $-CH_2-$ ];

$R_3$  and  $R_4$ , independently of one another, represent

- (i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and  $-S(O)_n-R$ ;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ ,  $NR_0$ ] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents (carbocyclic or heterocyclic) arylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3$ - $C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by  $C_3$ - $C_8$ -cycloalkyl, by  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O,  $S(O)_n$  or  $NR_0$ ] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by  $-CO-(O)_v-R$  and the integer v is 0 or 1;



wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case,  $R_0$  represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl,  $-SO_2-R$ , or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

$alk_1$  and  $alk_2$ , independently of one another, represent a single bond or lower alkylene;

$R_1$  represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

$R_2$  represents

(vi) a group selected from  $-CH(OH)-R$ ,  $-CO-R$ ,  $-NR_1-CO-O-R$ ,  $-NR_1-CO-R$ ,  $-NR_1-CO-NR_1-R$ ,  $-NR_1-SO_2-R$ ,  $-NR_1-SO_2-NR_1-R$ ,  $-SO_2-R$ ,  $-SO_2-NR_1-R$ , or  $-SO_2-NR_1-CO-R$ , [R being as defined below and  $R_1$  being as defined above, or the group  $-N(R)(R_1)$  represents amino which is disubstituted by lower alkylene (which may be interrupted by O,  $S(O)_n$  or  $NR_0$ ) or which is disubstituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula  $-X_1(X_2)(X_3)$  wherein, (a) if  $X_1$  is  $-CH-$ ,  $X_2$  together with  $X_3$  represent a structural element of formula  $-X_4-(CO)_p-(CH_2)_o-$ ,  $-(CH_2)_q-X_4-(CO)_p-(CH_2)_r-$ , or  $-(CH_2)_s-X_4-CO-(CH_2)_t-$ ; or, (b) if  $X_1$  is  $-N-$ ,  $X_2$  together with  $X_3$  represent a structural element of formula  $-CO-(CH_2)_u-$ ; [ $X_4$  being  $-CH_2-$ ,  $-N(R_1)-$  or  $-O-$ ; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0,  $X_4$  is different from  $-CH_2-$ ];

$R_3$  and  $R_4$ , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and  $-S(O)_n-R$ ;

R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, or NR<sub>0</sub>] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

- (i) halogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iv) amino, substituted amino;
- (v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolyl, isoquinolyl, or quinazolinyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O,

$S(O)_n$  or  $NR_0$ ] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by  $-CO-(O)_v-R$  and the integer  $v$  is 0 or 1;

wherein, in each case, the integer  $n$  is 0, 1 or 2;

wherein, in each case,  $R_0$  represents hydrogen or lower alkyl;

wherein, in each case,  $R$  represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which  $alk_1$  and  $alk_2$ , independently of one another, represent a single bond or lower alkylene;

$R_1$  represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

$R_2$  represents

(vi) a group selected from  $-CH(OH)-R$ ,  $-CO-R$ ,  $-NR_1-CO-R$ ,  $-NR_1-SO_2-R$ ,  $-NR_1-SO_2-NR_1-R$ ,  $-SO_2-R$ ,  $-SO_2-NR_1-R$ , or  $-SO_2-NR_1-CO-R$ , [ $R$  being as defined below and  $R_1$  being as defined above, or the group  $-N(R)(R_1)$  represents amino which is di-substituted by lower alkylene {which may be interrupted by O or  $NR_0$ } or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula  $-X_1(X_2)(X_3)$  wherein, (a) if  $X_1$  is  $-CH-$ ,  $X_2$  together with  $X_3$  represent a structural element of formula  $-X_4-(CO)_p-(CH_2)_o-$ ,  $-(CH_2)_q-X_4-(CO)_p-(CH_2)_r-$ , or  $-(CH_2)_s-X_4-CO-(CH_2)_t-$ ; or, (b) if  $X_1$  is  $-N-$ ,  $X_2$  together with  $X_3$  represent a structural element of formula  $-CO-(CH_2)_u-$ ; [ $X_4$  being  $-CH_2-$ ,  $-N(R_1)-$  or  $-O-$ ; the integer  $o$  is 3-5; the integer  $p$  is 0 or 1; the integer  $q$  is 1 or 2; the integer  $r$  is 1; the integer  $s$  is 1 or 2; the integer  $t$  is 1 or 2; the integer  $u$  is 3-5; with the proviso that, if the integer  $p$  is 0,  $X_4$  is different from  $-CH_2-$ ];

$R_3$  and  $R_4$ , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: lower alkoxy, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, and substituted carbamoyl;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ , or  $NR_0$ ];

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene which, in each case, is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, lower alkanoyloxy, or lower alkanoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) substituted amino;

(v) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl represents (phenyl-, naphthyl- or pyridyl)-lower alkoxy-carbonyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkyl represents phenyl-, naphthyl- or pyridyl-lower alkyl;

wherein, in each case, (carbocyclic or heterocyclic) aryl-oxy represents phenoxy, naphthyloxy, or pyridyloxy;

wherein, in each case, (carbocyclic or heterocyclic) aryl-lower alkanoyl represents (phenyl-, naphthyl- or pyridyl)-lower alkanoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-

cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk<sub>1</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl or lower alkyl which is substituted by lower alkoxy-carbonyl;

R<sub>2</sub> represents a group selected from -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R being lower alkyl, lower alkoxy-lower alkyl, phenyl, or naphthyl, and the group -N(R)(R<sub>1</sub>) represents amino which is mono-substituted by lower alkyl or by lower alkoxy-lower alkyl, or which is di-substituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene (which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or lower alkyl)];

(vi) carbamoyl;

R<sub>3</sub> represents hydrogen, lower alkyl which is unsubstituted or substituted by C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, by phenyl, or by di-lower alkylamino, or represents C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, hydroxy, and carbamoyl, or represents indazolyl;

R<sub>4</sub> represents hydrogen or lower alkyl which is unsubstituted or substituted by lower alkoxy-carbonyl; or

R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, or oxy-lower alkylene-oxy, or represents naphthylene;

wherein the benzo ring A is unsubstituted or substituted a substituent selected from the group consisting of: halogen, nitro, amino, di-lower alkylamino, lower alkyl, lower alkoxy,

lower alkoxy-lower alkoxy, lower alkoxy-lower alkyl, di-(lower alkyl)-amino-lower alkyl, phenyl, and lower alkanoyl.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk<sub>1</sub> represents a single bond;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen or lower alkyl;

R<sub>2</sub> represents

(iv) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene (which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or lower alkyl)];

R<sub>3</sub> represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R<sub>4</sub> represents (i) hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, or lower alkoxy;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, halo-lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk<sub>1</sub> represents a single bond;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen or lower alkyl;

R<sub>2</sub> represents

(iv) a group selected from -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R<sub>1</sub> being as defined below, or the group -N(R)(R<sub>1</sub>) represents amino which is mono-substituted by lower alkyl, by

hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene {which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or lower alkyl};

R<sub>3</sub> represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R<sub>4</sub> represents (i) hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, halo-lower alkoxy, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk<sub>1</sub> represents a single bond;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen or lower alkyl;

R<sub>2</sub> represents

(iv) a group selected from -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl, R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene {which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or lower alkyl}];

R<sub>3</sub> represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R<sub>4</sub> represents (i) hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, halo-lower alkoxy, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk<sub>1</sub> represents a single bond;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>- or C<sub>2</sub>-alkylene;

R<sub>1</sub> represents hydrogen;

R<sub>2</sub> represents -SO<sub>2</sub>-R or -SO<sub>2</sub>-NH-R and R being C<sub>1</sub>-C<sub>4</sub>-alkyl, especially methyl; and, in each case;

R<sub>3</sub> represents C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl-lower alkyl, or phenyl which is unsubstituted or is substituted by halogen, hydroxy, or lower alkoxy;

R<sub>4</sub> represents hydrogen; and

X represents 1,4-phenylene or 1,3-phenylene which is di-substituted by oxy-methylene-oxy;

wherein the benzo ring A is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk<sub>1</sub> and alk<sub>2</sub> both represent a single bond;

R<sub>1</sub> is hydrogen;

R<sub>4</sub> is hydrogen;

X is 1,4-phenylene;

R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially methoxy, and R<sub>3</sub> is phenyl which is substituted by hydroxy, especially 3-hydroxy-phenyl; or

R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially 2-methoxy-ethoxy, or 1-piperidino; and

R<sub>3</sub> is phenyl; and

the benzo ring A is unsubstituted or substituted in position 8 of the quinazoline ring by C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially methoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk<sub>1</sub> represents a single bond;

alk<sub>2</sub> represents C<sub>1</sub>-C<sub>3</sub>-alkylene; and

R<sub>2</sub> represents (iv) a group selected from -NH-SO<sub>2</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NH-R, [R being C<sub>1</sub>-C<sub>4</sub>-alkyl, or naphthyl, or the group -NH(R) represents amino which is mono-substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl, by hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, or by naphthyl, or which is di-substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl



or by C<sub>2</sub>-C<sub>6</sub>-alkylene {which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl}};

R<sub>1</sub> represents hydrogen;

R<sub>3</sub> represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, and oxy- C<sub>1</sub>-C<sub>4</sub>-alkylene-oxy; and

R<sub>4</sub> represents (i) hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, lower alkoxy-lower alkyl;

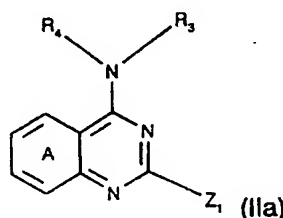
wherein the benzo ring A is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy.

The invention relates especially to a new compound of formula (I) or a salt thereof in which alk<sub>1</sub> is a single bond and alk<sub>2</sub> represents methylene; and R<sub>2</sub> is -SO<sub>2</sub>-NH-R and R is C<sub>1</sub>-C<sub>4</sub>-alkyl, especially methyl; the benzo ring A is unsubstituted; and, in each case, R<sub>1</sub> is hydrogen; R<sub>3</sub> is phenyl; R<sub>4</sub> is hydrogen; X is 1,4-phenylene.

The invention relates in particular to the novel compounds shown in the examples and to the modes of preparation described therein.

The invention relates to processes for the preparation of the compounds according to the invention. The preparation of new compounds of the formula (I) and their salts comprises, for example,

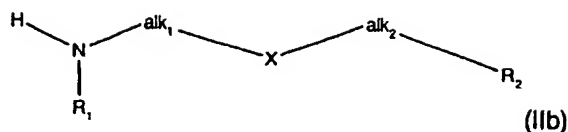
(a) reacting a compound of formula (IIa) or a salt thereof



in which Z<sub>1</sub> represents a leaving group,

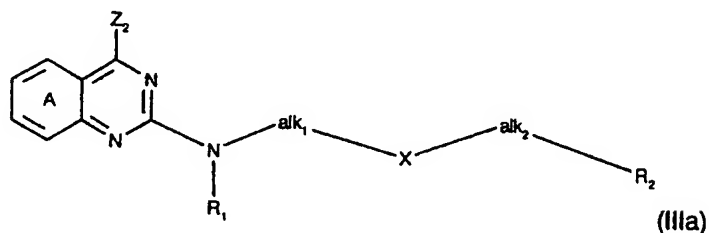
with a compound of formula (IIb) or a salt thereof

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or

(b) reacting a compound of formula (IIIa) or a salt thereof

in which  $Z_2$  is a leaving groupwith a compound of formula  $\text{HN}(\text{R}_3)(\text{R}_4)$  (IIb) or a salt thereof,

and, if desired, converting a compound (I) obtainable according to the process or in another manner, in free form or in salt form, into another compound (I),

separating a mixture of isomers obtainable according to the process and isolating the desired isomer and/or converting a free compound (I) obtainable according to the process into a salt or converting a salt of a compound (I) obtainable according to the process into the free compound (I) or into another salt.

The reactions described above and below in the variants are carried out in a manner known per se, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about  $-80^\circ\text{C}$  up to the boiling point of the reaction medium, preferably from about  $-10^\circ$  to about  $+200^\circ\text{C}$ , and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions. The person skilled in the pertinent art is especially referred to the methods as outlined in the working examples based upon which the person skilled in the art is enabled to carry out the manufacture of the compounds of formula (I).

Salts of starting materials which have at least one basic centre, for example of the formula IIIb, are appropriate acid addition salts, while salts of starting materials which have an acidic group, for example of the formula (IIb), are present as salts with bases, in each case as mentioned above in connection with corresponding salts of the formula (I).

A leaving group  $Z_1$  or  $Z_2$ , respectively, is, for example, reactive esterified hydroxy, or is  $R'-S(O)_u$  [the integer  $u$  being 0, 1 or 2 and  $R'$  being lower alkyl, halo-lower alkyl or aryl, such as methyl, trifluoromethyl or p-tolyl], or is lower alkoxy.

Reactive esterified hydroxyl  $Z_4$  is in particular hydroxyl esterified with a strong inorganic acid or organic sulfonic acid, for example halogen, such as fluorine, chlorine, or bromine, sulfonyloxy, such as hydroxysulfonyloxy, halosulfonyloxy, for example fluorosulfonyloxy,  $C_1$ - $C_7$ -alkane-sulfonyloxy which is unsubstituted or substituted, for example by halogen, for example methane- or trifluoromethanesulfonyloxy,  $C_5$ - $C_7$ -cycloalkanesulfonyloxy, for example cyclohexanesulfonyloxy, or benzenesulfonyloxy which is unsubstituted or substituted, for example by  $C_1$ - $C_7$ -alkyl or halogen, for example p-bromobenzene- or p-toluenesulfonyloxy. Preferred  $Z_1$  or  $Z_2$  is chloro, bromo or iodo, methanesulfonyloxy or trifluoromethanesulfonyloxy, or p-toluenesulfonyloxy, or methylthio or methoxy.

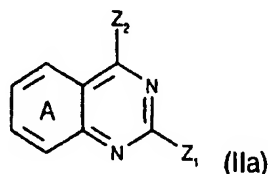
The reactions of process variants (a) and (b) are carried out, if necessary, in the presence of a base. Suitable bases are, for example, alkali metal hydroxides, hydrides, amides, alkanolates, carbonates, triphenylmethylenes, di-lower alkylamides, aminoalkylamides or lower alkylsilylamides, naphthaleneamines, lower alkylamines, basic heterocycles, ammonium hydroxides, and carbocyclic amines. Examples which may be mentioned are sodium hydroxide, sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium carbonate, lithium triphenylmethylenide, lithium diisopropylamide, potassium 3-(aminopropyl)amide, potassium bis(trimethylsilyl)amide, dimethylaminonaphthalene, di- or triethylamine, or ethyldiisopropylamine, N-methylpiperidine, pyridine, benzyldimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The starting material of formulae (IIa), (IIb), (IIIa), and (IIIb) is essentially known or is accessible analogously to preparation processes known per se.

Starting material of the formula (IIa) is, for example, described, for example, in US Patent No. 5,064,833.

The starting material of formula (IIb) in which  $R_2$  represents N-acylated or N-alkylated amino, such as a group of formula  $-NR_1-CO-O-R$ ,  $-NR_1-CO-R$ ,  $-NR_1-CO-NR_1-R$ ,  $-NR_1-SO_2-R$ ,  $-NR_1-SO_2-NR_1-R$ , or N-substituted amino, is accessible, for example, by N-acylating or by N-alkylating, respectively, a, preferably N-protected, compound of the formula  $NH(R_1)-alk_1-X-alk_2-Z_3$  (IIc) in which  $Z_3$  represents a group which is convertible to  $R_2$ , such as amino, carboxy, or hydroxy. Conventional protecting groups may be used, for example, t-butoxycarbonyl which will be split off after the N-acylation or the N-alkylation, respectively. The starting material of formula (IIb) in which  $R_2$  represents carbamoyl or N-substituted carbamoyl, or esterified carboxy, can be manufactured starting from a compound of formula (IIc) in which  $Z_3$  represents carboxy. The esterification or amidation can be carried out in a manner known per se. Starting from a compound of formula (IIc) in which  $Z_3$  is hydroxy, corresponding etherified or esterified derivatives are accessible using etherification or esterification methods known in the art.

The starting material of formula (IIIa) is accessible, for example, by selectively converting the 4- $Z_2$ -group into a group which is deactivated, for example, by selectively hydrolyzing a compound of formula (IIlc)



or a salt thereof to form a corresponding 4-hydroxy-compound which is in the next step reacted with a compound of formula (IIb) to introduce the corresponding side chain into position 2 of the quinazolin ring. Reactivation of the 4-position, for example, by reaction with a halogenating agent, such as  $POCl_3$ , leads to

corresponding compounds of formula (IIa).

A compound according to the invention which is obtainable by the process can be converted into another compound according to the invention in a manner known per se.

A compound according to the invention containing hydroxyl can be etherified by methods known per se. The etherification can be carried out, for example, using an alcohol, such as a substituted or unsubstituted lower alkanol, or a reactive ester thereof. Suitable reactive esters of the desired alcohols are, for example, those with strong inorganic or organic acids, such as corresponding halides, sulfates, lower alkanesulfonates or substituted or unsubstituted benzenesulfonates, for example chlorides, bromides, iodides, methane-, benzene- or p-toluenesulfonates. The etherification can be carried out, for example, in the presence of a base, an alkali metal hydride, hydroxide or carbonate, or of an amine. Conversely, corresponding ethers, such as lower alkoxy compounds, can be cleaved, for example, by means of strong acids, such as mineral acids, for example the hydrohalic acids hydrobromic or hydriodic acid, which may advantageously be present in the form of pyridinium halides, or by means of Lewis acids, for example halides of elements of main group III or the corresponding sub-groups. These reactions can be carried out, if necessary, with cooling or warming, for example in a temperature range from about -20° to about 100°C, in the presence or absence of a solvent or diluent, under inert gas and/or under pressure and, if appropriate, in a closed vessel.

Compounds according to the invention containing hydroxymethyl groups can be prepared, for example, starting from compounds containing corresponding carboxyl or esterified carboxyl, corresponding compounds being reduced in a manner known per se, for example by reduction with a hydride which, if desired, may be complex, such as a hydride formed from an element of the 1st and 3rd main groups of the periodic table of the elements, for example borohydride or aluminohydride, for example lithium borohydride, lithium aluminium hydride, diisobutylaluminium hydride (an additional reduction step using alkali metal cyanoborohydride, such as sodium cyanoborohydride, may be necessary), and

also diborane.

If an aromatic structural component is substituted by (lower) alkylthio (in  $S(O)_n$  -R n is 0), this can be oxidised in a customary manner to corresponding (lower) alkanesulfinyl or -sulfonyl. Suitable oxidising agents for the oxidation to the sulfoxide step are, for example, inorganic peracids, such as peracids of mineral acids, for example periodic acid or persulfuric acid, organic peracids, such as appropriate percarboxylic or persulfonic acids, for example performic, peracetic, trifluoroperacetic or perbenzoic acid or p-toluenepersulfonic acid, or mixtures of hydrogen peroxide and acids, for example a mixture of hydrogen peroxide with acetic acid.

The oxidation is commonly carried out in the presence of suitable catalysts, catalysts which can be mentioned being suitable acids, such as substituted or unsubstituted carboxylic acids, for example acetic acid or trifluoroacetic acid, or transition metal oxides, such as oxides of elements of sub-group VII, for example vanadium oxide, molybdenum oxide or tungsten oxide. The oxidation is carried out under mild conditions, for example at temperatures from about  $-50^{\circ}$  to about  $+100^{\circ}\text{C}$ .

The oxidation to the sulfone step may also be carried out appropriately at low temperatures using dinitrogen tetroxide as the catalyst in the presence of oxygen, just like the direct oxidation of (lower) alkylthio to (lower) alkanesulfonyl. However, in this case the oxidising agent is customarily employed in an excess.

If one of the variables contains amino, corresponding compounds of the formula (I), their tautomers or salts can be N-alkylated in a manner known per se; likewise, carbamoyl or radicals containing carbamoyl can be N-alkylated. The (aryl)alkylation is carried out, for example, using a reactive ester of an (aryl) $C_1$ - $C_7$ alkyl halide, for example a bromide or iodide, (aryl) $C_1$ - $C_7$ alkylsulfonate, for example methanesulfonate or p-toluenesulfonate, or a di- $C_1$ - $C_7$ alkyl sulfate, for example dimethyl sulfate, preferably under basic conditions, such as in the presence of sodium hydroxide solution or potassium hydroxide solution, and advantageously in the presence of a phase transfer catalyst, such as

tetrabutylammonium bromide or benzyltrimethylammonium chloride, where, however, stronger basic condensing agents, such as alkali metal amides, hydrides or alkoxides, for example sodium amide, sodium hydride or sodium ethoxide, may be necessary. Amino can also be acylated in a manner known per se.

In compounds of the formula (I) which contain an esterified or amidated carboxyl group as a substituent, a group of this type can be converted into a free carboxyl group, for example by means of hydrolysis, for example in the presence of a basic agent, or of an acidic agent, such as a mineral acid. *tert*-Butyloxycarbonyl, for example, can furthermore be converted into carboxyl, for example in a manner known per se, such as treating with trihaloacetic acid, such as trifluoroacetic acid, and benzyloxycarbonyl can be converted into carboxyl, for example by catalytic hydrogenation in the presence of a hydrogenation catalyst, for example in the manner described below.

Furthermore, in compounds of the formula (I) which contain a carboxyl group as a substituent, this can be converted into an esterified carboxyl group, for example, by treating with an alcohol, such as a lower alkanol, in the presence of a suitable esterifying agent, such as an acid reagent, for example an inorganic or organic acid or a Lewis acid, for example zinc chloride, or a condensing agent which binds water, for example a carbodiimide, such as *N,N'*-dicyclohexylcarbodiimide, or by treating with a diazo reagent, such as with a diazo-lower alkane, for example diazomethane. This can also be obtained if compounds of the formula (I) in which the carboxyl group is present in free form or in salt form, such as ammonium salt or metal salt form, for example alkali metal salt form, such as sodium salt or potassium salt form, are treated with a reactive ester of a (C<sub>1</sub>-C<sub>7</sub>)alkyl halide, for example methyl or ethyl bromide or iodide, or an organic sulfonic acid ester, such as an appropriate (C<sub>1</sub>-C<sub>7</sub>)alkyl ester, for example methyl or ethyl methanesulfonate or *p*-toluenesulfonate.

Compounds of the formula (I) which contain an esterified carboxyl group as a substituent can be transesterified into other ester compounds of the formula (I) by transesterification, for example by treating with an alcohol, customarily a higher

appropriate alcohol than that of the esterified carboxyl group in the starting material, in the presence of a suitable transesterifying agent, such as a basic agent, for example an alkali metal (C<sub>1</sub>-C<sub>7</sub>)alkanoate, (C<sub>1</sub>-C<sub>7</sub>)alkanolate or alkali metal cyanide, such as sodium acetate, sodium methoxide, sodium ethoxide, sodium tert-butoxide or sodium cyanide, or a suitable acid agent, if appropriate with removal of the resulting alcohol, for example by distillation. Appropriate, so-called activated esters of the formula (I) which contain an activated esterified carboxyl group as a substituent may also be used as starting materials (see below), and these may be converted into another ester by treating with a (C<sub>1</sub>-C<sub>7</sub>)alkanol.

In compounds of the formula (I) which contain the carboxyl group as a substituent, this can also first be converted into a reactive derivative, such as an anhydride, including a mixed anhydride, such as an acid halide, for example an acid chloride (for example by treating with a thionyl halide, for example thionyl chloride), or an anhydride using a formic acid ester, for example a (C<sub>1</sub>-C<sub>7</sub>)alkyl ester (for example by treating a salt, such as an ammonium or alkali metal salt, with a haloformic acid ester, such as a chloroformic acid ester, such as a (C<sub>1</sub>-C<sub>7</sub>)alkyl ester), or into an activated ester, such as a cyanomethyl ester, a nitrophenyl ester, for example a 4-nitrophenyl ester, or a polyhalophenyl ester, for example a pentachlorophenyl ester (for example by treating with an appropriate hydroxyl compound in the presence of a suitable condensing agent, such as N,N'-dicyclohexylcarbodiimide), and then a reactive derivative of this type can be reacted with an amine and in this way amide compounds of the formula (I) which contain an amidated carboxyl group as a substituent can be obtained. In this case, these can be obtained directly or via intermediate compounds; thus, for example, an activated ester, such as a 4-nitrophenyl ester, of a compound of the formula (I) containing a carboxyl group can first be reacted with a 1-unsubstituted imidazole and the 1-imidazolylcarbonyl compound obtained in this way brought to reaction with an amine. However, other non-activated esters, such as (C<sub>1</sub>-C<sub>7</sub>)alkyl esters of compounds of the formula (I), which contain, for example, (C<sub>2</sub>-C<sub>8</sub>)alkoxycarbonyl as a substituent, can also be brought to reaction with amines.



If an aromatic ring contains a hydrogen atom as a substituent, the latter can be replaced by a halogen atom with the aid of a halogenating agent in a customary manner, for example brominated with bromine, hypobromic acid, acyl hypobromites or other organic bromine compounds, for example N-bromosuccinimide, N-bromoacetamide, N-bromophthalimide, pyridinium perbromide, dioxane dibromide, 1,3-dibromo-5,5-dimethylhydantoin or 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one, or chlorinated with elemental chlorine, for example in a halogenated hydrocarbon, such as chloroform, and with cooling, for example from down to about  $-10^{\circ}$  to about  $+100^{\circ}\text{C}$ .

If an aromatic ring in the compounds according to the invention contains an amino group, this can be diazotized in a customary manner, for example by treating with a nitrite, for example sodium nitrite, in the presence of a suitable protonic acid, for example a mineral acid, the reaction temperature advantageously being kept below about  $5^{\circ}\text{C}$ . The diazonium group present in the salt form and obtainable in this way can be substituted by analogous processes, for example as follows: by the hydroxyl group analogously to the boiling-out of phenol in the presence of water; by an alkoxy group by treating with an appropriate alcohol, energy having to be added; by the fluorine atom analogously to the Schiemann reaction in the thermolysis of corresponding diazonium tetrafluoroborates; by the halogen atoms chlorine, bromine or iodine and also the cyano group analogously to the Sandmeyer reaction in the reaction with corresponding Cu(I) salts, initially with cooling, for example to below about  $5^{\circ}\text{C}$ , and then heating, for example to about  $60^{\circ}$  to about  $150^{\circ}\text{C}$ .

If the compounds of the formula (I) contain unsaturated radicals, such as (lower) alkenyl or (lower) alkynyl groups, these can be converted into saturated radicals in a manner known per se. Thus, for example, multiple bonds are hydrogenated by catalytic hydrogenation in the presence of hydrogenation catalysts, suitable catalysts for this purpose being, for example, nickel, such as Raney nickel, and noble metals or their derivatives, for example oxides, such as palladium or platinum oxide, which may be applied, if desired, to support materials, for example to carbon or calcium carbonate. The hydrogenation may preferably be carried out at pressures between 1 and about 100 at and at room temperature

between about -80° to about 200°C, in particular between room temperature and about 100°C. The reaction is advantageously carried out in a solvent, such as water, a lower alkanol, for example ethanol, isopropanol or n-butanol, an ether, for example dioxane, or a lower alkanecarboxylic acid, for example acetic acid.

Furthermore, in compounds of the formula (I) in which, for example, one of the aryl radicals contains halogen, such as chlorine, halogen can be replaced by reaction with a substituted or unsubstituted amine, an alcohol or a mercaptan.

The invention relates in particular to the processes described in the examples.

Salts of compounds of the formula (I) can be prepared in a manner known per se. Thus, for example, acid addition salts of compounds of the formula (I) are obtained by treating with an acid or a suitable ion exchange reagent. Salts can be converted into the free compounds in a customary manner, and acid addition salts can be converted, for example, by treating with a suitable basic agent.

Depending on the procedure and reaction conditions, the compounds according to the invention having salt-forming, in particular basic properties, can be obtained in free form or preferably in the form of salts.

In view of the close relationship between the novel compound in the free form and in the form of its salts, in the preceding text and below the free compound or its salts may correspondingly and advantageously also be understood as meaning the corresponding salts or the free compound.

The novel compounds including their salts of salt-forming compounds can also be obtained in the form of their hydrates or can include other solvents used for crystallization.

Depending on the choice of the starting materials and procedures, the novel compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, such as antipodes, or as isomer mixtures, such as racemates, diastereoisomer mixtures or racemate

mixtures, depending on the number of asymmetric carbon atoms. For example, compounds of the formula (I) in which  $-\text{alk}_2-\text{R}_2$  or  $-\text{NR}_3\text{R}_4$  have an asymmetric C atom.

Racemates and diastereomer mixtures obtained can be separated into the pure isomers or racemates in a known manner on the basis of the physicochemical differences of the components, for example by fractional crystallization.

Racemates obtained may furthermore be resolved into the optical antipodes by known methods, for example by recrystallization from an optically active solvent, chromatography on chiral adsorbents, with the aid of suitable microorganisms, by cleavage with specific immobilized enzymes, via the formation of inclusion compounds, for example using chiral crown ethers, only one enantiomer being complexed, or by conversion into diastereomeric salts, for example by reaction of a basic final substance racemate with an optically active acid, such as a carboxylic acid, for example tartaric or malic acid, or sulfonic acid, for example camphorsulfonic acid, and separation of the diastereomer mixture obtained in this manner, for example on the basis of its differing solubilities, into the diastereomers from which the desired enantiomer can be liberated by the action of suitable agents. The more active enantiomer is advantageously isolated.

The invention also relates to those embodiments of the process, according to which a compound obtainable as an intermediate in any step of the process is used as a starting material and the missing steps are carried out or a starting material in the form of a derivative or salt and/or its racemates or antipodes is used or, in particular, formed under the reaction conditions.

In the process of the present invention, those starting materials are preferably used which lead to the compounds described as particularly useful at the beginning. The invention likewise relates to novel starting materials which have been specifically developed for the preparation of the compounds according to the invention, to their use and to processes for their preparation, the variables  $\text{alk}_1$ ,  $\text{alk}_2$ ,  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ , and X having the meanings indicated for the preferred compound groups of the formula (I) in each case.

The invention likewise relates to pharmaceutical preparations which contain the compounds according to the invention or pharmaceutically acceptable salts thereof as active ingredients, and to processes for their preparation.

The pharmaceutical preparations according to the invention which contain the compound according to the invention or pharmaceutically acceptable salts thereof are those for enteral, such as oral, furthermore rectal, and parenteral administration to (a) warm-blooded animal(s), the pharmacological active ingredient being present on its own or together with a pharmaceutically acceptable carrier. The daily dose of the active ingredient depends on the age and the individual condition and also on the manner of administration.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 80%, preferably from about 20 % to about 60 %, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

Suitable carriers are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, furthermore binders, such as starch paste, using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, such as the abovementioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate; auxiliaries are primarily glidants, flow-regulators and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as

magnesium or calcium stearate, and/or polyethylene glycol. Sugar-coated tablet cores are provided with suitable coatings which, if desired, are resistant to gastric juice, using, inter alia, concentrated sugar solutions which, if desired, contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of gastric juice-resistant coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colorants or pigments, for example to identify or to indicate different doses of active ingredient, may be added to the tablets or sugar-coated tablet coatings.

Other orally utilizable pharmaceutical preparations are hard gelatin capsules, and also soft closed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The hard gelatin capsules may contain the active ingredient in the form of granules, for example in a mixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, if desired, stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it also being possible to add stabilizers.

Suitable rectally utilizable pharmaceutical preparations are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Furthermore, gelatin rectal capsules which contain a combination of the active ingredient with a base substance may also be used. Suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable preparations for parenteral administration are primarily aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and furthermore suspensions of the active ingredient, such as appropriate oily injection suspensions, using suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which contain viscosity-increasing substances, for example sodium

carboxymethylcellulose, sorbitol and/or dextran, and, if necessary, also stabilizers.

The dose of the active ingredient depends on the warm-blooded animal species, the age and the individual condition and on the manner of administration. In the normal case, an approximate daily dose of about 10 mg to about 250 mg is to be estimated in the case of oral administration for a patient weighing approximately 75 kg .

The following examples illustrate the invention described above; however, they are not intended to limit its extent in any manner. Temperatures are indicated in degrees Celsius.

The following examples illustrate the invention.

Abbreviations as used:

HCl	hydrochloric acid
NaOH	sodium hydroxide
min	minute(s)
h	hour(s)
m.p.	melting point
FAB-MS	Fast Atom Bombardment Mass Spectroscopy
Rf	retention factor on a thin layer chromatography plate

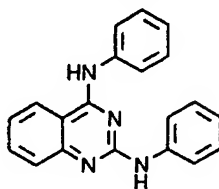
Solvent Systems for Thin-Layer Chromatography:

A1:	dichloromethane / methanol	9:1
A2:	dichloromethane / methanol	19:1
A3:	dichloromethane / methanol / ammonium hydroxide	90:10: 1
B1:	toluene / ethylacetate	1:1
B2:	toluene / ethylacetate	10:1
B3:	toluene / hexanes	1:1
B4:	toluene	
C1:	hexanes / ethylacetate	4:1

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C2:	hexanes / ethylacetate	3:1
C3:	hexanes / ethylacetate	2:1
C4:	hexanes / ethylacetate	1:1
D1:	dichloroethane / methanol / water / acetic acid	170:26:3:1
D3:	toluene / ethanol / ammonium hydroxide	90:20: 1
E1:	ethylacetate / ethanol / ammonium hydroxide	6: 3: 1

Example 1: 2,4-Diphenylamino-quinazoline hydrochloride



2-Chloro-4-phenylamino-quinazoline (7.671 g) and aniline (3.627 g) are heated up for 3 min to produce a melt which is dissolved in methanol. The product is obtained as its hydrochloride salt upon addition of a slight excess of 4N HCl in dioxane. Recrystallization from isopropanol yields 2,4-diphenylamino-quinazoline hydrochloride, m.p. 319 - 320°C.

The starting material can be prepared, for example, as follows:

a) 2-Chloro-4-phenylamino-quinazoline

A solution of 2,4-dichloro-quinazoline (15 g), N,N-diisopropyl-ethylamine (24.9 ml) and aniline (7.5 ml) in isopropanol (75 ml) is heated to reflux for 45 min. The cold reaction mixture is filtered and the filtrate is concentrated *in vacuo*. The residue is crystallized from diethylether- toluene (1:1) to give 2-chloro-4-phenylamino-quinazoline, m.p. 194 - 196°C.

b) 2,4-Dichloro-quinazoline

N,N-Dimethylaniline (114.0 g) is added slowly to a solution of 1H,3H-quinazolin-2,4-dione (146.0 g) in phosphorousoxychloride (535.4 ml) while this mixture is heated up to 140°C. After completion of the addition reflux is continued for 20 h. The reaction mixture is filtered and evaporated to give a residue which is added to ice and water. The product is extracted with dichloromethane and crystallized from diethylether and petroleum diethylether to yield 2,4-dichloro-quinazoline, m.p. 115 - 116°C.

**Example 2: 2-(4-Methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride**

A mixture of 2-chloro-4-phenylamino-quinazoline (0.767 g) and 4-methoxy-aniline (0.493 g) is heated up for 3 min to produce a melt which is dissolved in isopropanol (10 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 296 - 297°C.

**Example 3: 2-(4-Fluoro-phenylamino)-4-phenylamino-quinazoline hydrochloride**

A mixture of 2-chloro-4-phenylamino-quinazoline (0.307 g) and 4-fluoro-aniline (0.144 ml) is heated for 2 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-fluoro-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 322 - 324°C.

**Example 4: 2-(4-Phenyl-phenylamino)-4-phenylamino-quinazoline hydrochloride**

A mixture of 2-chloro-4-phenylamino-quinazoline (0.256 g) and 4-amino-biphenyl (0.211 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (3 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-phenyl-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 306 - 307°C.

**Example 5: 2-[4-(N,N-Dimethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride**

A mixture of 2-chloro-4-phenylamino-quinazoline (0.767 g) and 4-amino-N,N-dimethyl-aniline (0.545 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (10 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[4-(N,N-dimethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 281 - 283°C.

**Example 6: 2-(3,4-Dimethoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride**

A mixture of 2-chloro-4-phenylamino-quinazoline (0.380 g) and 3,4-dimethoxy-aniline (0.306 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (5 ml). 4N HCl in



dioxane (0.1 ml) is added. Crystallization yields 2-(3,4-dimethoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 250 - 251°C.

Example 7: 2-[4-(N,N-Diethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.767 g) and 4-amino-N,N-diethyl-aniline (0.657 g) is heated for 2 min to produce a melt which is dissolved in acetonitrile (9 ml) and 4N HCl in dioxane (1 ml). The precipitate is recrystallized from methanol and acetonitrile to yield 2-[4-(N,N-diethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 209 - 211°C.

Example 8: 2-[4-(Benzyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.380 g) and 4-benzyloxy-aniline (0.400 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (5 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-[4-(benzyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride, m.p. 225 - 227°C.

Example 9: 2-(4-Amino-phenylamino)-4-phenylamino-quinazoline dihydrochloride

A solution of 2-(4-nitro-phenylamino)-4-phenylamino-quinazoline (0.536 g) in N,N-dimethylformamide (15 ml) is hydrogenated in the presence of Raney nickel (3 times 0.2 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The obtained residue is dissolved in isopropanol - methanol (1:1) (10 ml) and treated with 4N HCl in dioxane (1 ml). Crystallization yields 2-(4-amino-phenylamino)-4-phenylamino-quinazoline dihydrochloride, m.p. 311 - 312°C.

The starting material can be prepared, for example, as follows:

2-(4-Nitro-phenylamino)-4-phenylamino-quinazoline

A mixture of 2-chloro-4-phenylamino-quinazoline (0.511 g) and 4-nitro-aniline (0.332 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in

dioxane (0.1 ml) is added. Crystallization yields 2-(4-nitro-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 348-350°C.

Example 10: 2-[3-(N,N-Dimethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.384 g) and 3-amino-N,N-dimethylaniline (0.272 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[3-(N,N-dimethylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 280 - 283°C.

Example 11: 2-[4-(N,N-Dipropylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (1.40 g) and 4-amino-N,N-dipropylaniline (1.37 g) is heated for 5 min to produce a melt which is dissolved in isopropanol (16 ml). 4N HCl in dioxane (1.5 ml) is added. Crystallization yields 2-[4-(N,N-dipropylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 270 - 272°C.

The starting material can be prepared, for example, as follows:

a) 4-Nitro-N,N-dipropyl-aniline

A mixture of 4-fluoro-1-nitro-benzene (1.41 g) and dipropylamine (6.86 ml) is heated in an autoclave for 8 h to 160°C. The product is added to 2N aqueous NaOH and extracted with ethylacetate to yield 4-nitro-N,N-dipropyl-aniline as a yellowish oil, Rf (C3) 0.59.

b) 4-Amino-N,N-dipropyl-aniline

A solution of 4-nitro-N,N-dipropyl-aniline (2.2 g) in ethanol (50 ml) is hydrogenated in the presence of Raney nickel (3 times 0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to yield of 4-amino-N,N-dipropyl-aniline as an oil, Rf (C3) 0.09.

Example 12: 2-(4-Cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.511 g) and 4-amino-benzonitrile (0.315 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 340 - 342°C.

Example 13: 2-[4-(2-Pyridylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.384 g) and 4-(2-pyridylamino)-aniline (0.334 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[4-(2-pyridylamino)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 225 - 226°C.

The starting material can be prepared, for example, as follows:

4-(2-Pyridylamino)-aniline

A solution of N-(4-nitrophenyl)-2-pyridinamine (*Annali di Chimia* 1956, 46, 406) (5.38 g) in ethanol (100 ml) is hydrogenated in the presence of palladium on charcoal 5% (0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to yield 4-(2-pyridylamino)-aniline, m.p. 120 - 122°C.

Example 14: 2-[4-(Aminomethyl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A solution of 2-(4-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride (5.42 g) in ethanol (20 ml) is hydrogenated in the presence of Raney nickel (0.3 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is treated with 4N HCl in dioxane (2 ml) and crystallized from isopropanol and methanol to yield of 2-[4-(aminomethyl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 320 - 322°C.

Example 15: 2-[3-(Aminomethyl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A solution of 2-(3-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride (0.939 g) in ethanol (40 ml) is hydrogenated in the presence of Raney nickel (0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is treated with 4N HCl in dioxane (3 ml) and crystallized from isopropanol and methanol to yield of 2-[3-(aminomethyl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, m.p. 280 - 282°C.

The starting material can be prepared, for example, as follows:

2-(3-Cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.770 g) and 3-amino-benzonitrile (0.460 g) is heated for 5 min to produce a melt which is dissolved in isopropanol (10 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(3-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 326 - 328°C.

Example 16: 2-(4-Hydroxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

A solution of 2-[4-(phenylmethyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride (2.15 g) in ethanol (50 ml) is hydrogenated in the presence of palladium on charcoal 5% (0.6 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is crystallized from isopropanol and methanol to yield 2-(4-hydroxy-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 309 - 310°C.

The starting material can be prepared, for example, as follows:

2-[4-(Phenylmethyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (1.28 g) and 4-benzyloxy-aniline (1.33 g) is heated for 5 min to produce a melt which is dissolved in isopropanol (15 ml). 4N HCl in dioxane (0.2 ml) is added. Crystallization yields 2-[4-(phenylmethyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride, m.p. 225 - 226°C.

Example 17: 2-[4-(3-Cyclohexyl-propyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

A suspension of 2-(4-hydroxy-phenylamino)-4-phenylamino-quinazoline hydrochloride (292 g), 3-iodopropyl-cyclohexane (EP 518,426) (0.212 g), and potassium carbonate (0.221 g) in acetonitrile (20 ml) is heated to reflux for 5 h. The reaction mixture is filtered and the filtrate concentrated *in vacuo*. The residue is added to 2N NaOH and extracted with ethylacetate. The crude product is treated with 4N HCl in dioxane and crystallized from isopropanol and acetonitrile to yield

2-[4-(3-cyclohexyl-propyloxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride, m.p. 223 - 224°C.

**Example 18: 2,4-Di-(4-methoxy-phenylamino)-quinazoline hydrochloride**

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.50 g) and 4-methoxy--aniline (0.28 g) is heated for 4 min to produce a melt which is dissolved in isopropanol (5 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2,4-di-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 282 - 284°C.

The starting material can be prepared, for example, as follows:

**2-Chloro-4-(4-methoxy-phenylamino)-quinazoline**

A solution of 2,4-dichloro-quinazoline (4.0 g), N,N-diisopropyl-ethylamine (6.6 ml) and 4-methoxy-aniline (2.5 g) in isopropanol (20 ml) is heated to reflux for 20 min. The reaction mixture is concentrated *in vacuo* and the residue is added to 2N sodium bicarbonate and extracted with ethylacetate. Crystallization from toluene gives 2-chloro-4-(4-methoxy-phenylamino)-quinazoline, m.p. 150 - 152°C.

**Example 19: 2-(4-Cyano-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride**

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.429 g) and 4-amino-benzonitrile (0.236 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-cyano-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 274 - 276°C.

The starting material can be prepared, for example, as follows:

2-Chloro-4-(3-methoxy-phenylamino)-quinazoline

A solution of 2,4-dichloro-quinazoline (6.0 g), N,N-diisopropyl-ethylamine (9.95 ml), and 3-methoxy-aniline (3.68 ml) in isopropanol (30 ml) is heated to reflux for 30 min. The reaction mixture is concentrated *in vacuo* and the residue is added to 2N NaOH and extracted with ethylacetate. Crystallization from toluene gives 2-chloro-4-(3-methoxy-phenylamino)-quinazoline, m.p. 176 - 178°C.

Example 20: 2-[4-(N,N-Diethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.286 g) and 4-amino-N,N-diethyl-aniline (0.214 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (3 ml) and 4N HCl in dioxane (1 ml). The precipitate is recrystallized from isopropanol and diethylether to yield 2-[4-(N,N-diethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 239 - 241°C.

Example 21: 2-(4-Cyclohexyl-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.286 g) and 4-cyclohexyl-aniline (0.228 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (3 ml) and 4N HCl in dioxane (0.1 ml). Recrystallisation from isopropanol and diethylether yields 2-(4-cyclohexyl-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 240 - 242°C.

Example 22: 2-(4-Methoxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.286 g) and 4-methoxy-aniline (0.160 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (3 ml) and 4N HCl in dioxane (0.1 ml). Crystallization from isopropanol and diethylether yields

2-(4-methoxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 271 - 272°C.

**Example 23: 2-[4-(Aminomethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride**

A solution of 2-(4-cyano-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride (0.38 g) in ethanol (20 ml) is hydrogenated in the presence of Raney nickel (0.2 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is dissolved in methanol and treated with 4N HCl in dioxane (1 ml) and crystallized from isopropanol and methanol to yield 2-[4-(aminomethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 215 - 217°C.

**Example 24: 2-(4-N,N-Diethylamino-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride**

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.429 g) and 4-amino-N,N-diethyl-aniline (0.320 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (5 ml) and 4N HCl in dioxane (1 ml). Crystallization from isopropanol and acetonitrile yields 2-(4-N,N-diethylamino-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 238 - 240°C.

**Example 25: 2-[4-(N,N-Dipropylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride**

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.57 g) and 4-amino-N,N-dipropyl-aniline (0.50 g) is heated for 4 min to produce a melt which is dissolved in isopropanol (6 ml). 4N HCl in dioxane (1 ml) is added. Crystallization from isopropanol and acetonitrile yields 2-[4-(N,N-dipropylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 246 - 248°C.

**Example 26: 2-(4-Cyclohexyl-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride**

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.343 g) and 4-cyclohexyl-aniline (0.274 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml) and 4N HCl in dioxane (0.1 ml). Recrystallisation from isopropanol and diethylether yields 2-(4-cyclohexyl-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 301 - 302°C.

**Example 27: 2-(4-Hydroxy-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride**

A solution of 2-[4-(phenylmethyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride (0.582 g) in methanol (20 ml) is hydrogenated in the presence of palladium on charcoal 5% (0.12 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is crystallized from isopropanol and methanol to yield 2-(4-hydroxy-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 256 - 258°C.

The starting material can be prepared, for example, as follows:

**2-[4-(Phenylmethyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride**

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.571 g) and 4-benzyloxy-aniline (0.517 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (6 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-[4-(phenylmethyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 272 - 273°C.

**Example 28: 2-[4-(2-Pyridylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride**

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.256 g) and 4-(2-pyridylamino)-aniline (0.280 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Crystallization from methanol and isopropanol yields 2-[4-(2-pyridylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 240 - 242°C.



**Example 29: 2-[4-(N,N-Dimethylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride**

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (0.429 g) and 4-amino-N,N-dimethyl-aniline (0.273 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (5 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[4-(N,N-dimethylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 228 - 230°C.

**Example 30: 2-[4-(Piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride**

A mixture of 2-chloro-4-phenylamino-quinazoline (0.18 g) and N-(4-aminophenyl)-piperidine (0.164 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Recrystallization from ethanol and diethylether yields 2-[4-(piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, Rf (A1) 0.64.

**Example 31: 2-[4-(Benzyloxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride**

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (1.99 g) and 4-benzyloxy-aniline (1.80 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (6 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization from isopropanol and diethylether yields 2-[4-(benzyloxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 206 - 207°C.

**Example 32: 2-(4-Hydroxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride**

A solution of 2-[4-(benzyloxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride (1.80 g) in methanol (50 ml) is hydrogenated in the presence of palladium on charcoal 5% (0.36 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is crystallized from methanol

and acetonitrile to yield 2-(4-hydroxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 281 - 283°C.

**Example 33: 2-[3-(N,N-Dimethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride**

A mixture of 2-chloro-4-(3-methoxy-phenylamino)-quinazoline (0.57 g) and 3-amino-N,N-dimethyl-aniline (0.35 g) is heated for 4 min to produce a melt which is dissolved in isopropanol (6 ml). 4N HCl in dioxane (1 ml) is added. Crystallization yields 2-[3-(N,N-dimethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 197 - 199°C.

The following compounds are prepared, for example, in an analogous manner:

**Example 34: 2-(4-Chloro-phenylamino)-4-phenylamino-quinazoline hydrochloride**  
M.p. 325 - 326°C.

**Example 35: 2-(4-Methyl-phenylamino)-4-phenylamino-quinazoline hydrochloride**  
M.p. 294 - 296°C.

**Example 36: 2-(3-Methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride**  
M.p. 298 - 299°C.

**Example 37: 2-(2-Methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride**  
M.p. 256 - 258°C.

**Example 38: 2-(4-Nitro-phenylamino)-4-phenylamino-quinazoline hydrochloride**  
M.p. 348 - 350°C.

**Example 39: 2,4-Di-(3-methoxy-phenylamino)-quinazoline hydrochloride**  
M.p. 232 - 233°C.

**Example 40: 2-[4-(Benzyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride**

M.p. 272 - 273°C.

Example 41: 2-[4-(Aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride

M.p. 308 - 311°C.

Example 42: 2-[4-(Piperidin-1-yl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 230 - 233°C.

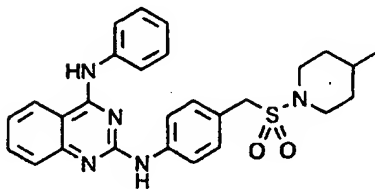
Example 43: 2-[4-(Piperidin-1-yl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 282 - 285°C.

Example 44: N-Methyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane sulfonamide hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (0.92 g) (prepared as described in Example 1a and N-methyl-(4-aminophenyl)-methanesulfonamide (0.80 g) (prepared as described in *Tetrahedron Letters* 1992, 33, 8011) in 10 ml of isopentylalcohol is stirred under nitrogen at 170 °C for 15 min in a sealed vessel. The warm reaction mixture is diluted with 10 ml ethanol and the hydrochloride salt, which is crystallizing on cooling, is filtered off to yield N-methyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 259 - 263°C; Rf (A2) 0.11.

Example 45: N-2-[4-(4-Methyl-piperidine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine hydrochloride



In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.312 g) and N-(4-methyl-piperidine-1-sulfonylmethyl)-phenylamine (0.36 g) are reacted together to give after recrystallisation from dimethylformamide and diethylether N-2-[4-(4-methyl-piperidine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine hydrochloride as yellow crystals melting at 234 - 238°C; Rf (A2) 0.14; FAB-MS: (M+H)<sup>+</sup> = 488.

The starting material can be prepared, for example, as follows:

a) 4-Methyl-1-(4-nitro-benzylsulfonyl)-piperidine

A solution of (4-nitrophenyl)-methanesulfonylchloride (3.54 g) (prepared as described in *J. Am. Chem. Soc.* 1937,59,1837) in dichloromethane (50 ml) is added to a solution of 4-methyl-piperidine (3.8 ml) in 25 ml of dichloromethane at 0 - 5°C and the reaction mixture is stirred for 20 h at room temperature. The solvent is evaporated and the residue is dissolved in ethylacetate (100 ml) and washed with water. The organic layer is dried, concentrated and the crude product is recrystallised from ethylacetate and diethylether to yield 4-methyl-1-(4-nitro-benzylsulfonyl)-piperidine as white crystals melting at 136 - 138°C; Rf (B1) 0.54.

b) 4-(4-methyl-piperidine-1-sulfonylmethyl)-phenylamine

A solution of 4-methyl-1-(4-nitro-phenylmethanesulfonyl)-piperidine (3.8 g) in methanol (300 ml) is hydrogenated over 5% palladium on carbon (0.75 g) at 3 atm. and 25°C for 2 h. The reaction mixture is filtered, partly concentrated and crystallized by the addition of diethylether to yield 4-(4-methyl-piperidine-1-sulfonylmethyl)-phenylamine, melting at 138 - 139°C; Rf (B1) 0.39.

Example 46: N-2-[4-(N-Methyl-piperazine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine dihydrochloride

In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.228 g) and N-[N-methyl-piperazinyl-(4-aminophenyl)]-methanesulfonamide monohydrochloride (0.3 g) are reacted together to give N-2-[4-(N-methyl-piperazine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine dihydrochloride as yellow crystals melting at 206 - 209°C; Rf (A2) 0.05.

The starting material can be prepared, for example, as follows:

a) 1-Methyl-4-(4-nitro-phenylmethanesulfonyl)-piperazine

In a procedure analogous to that of Example 45a (4-nitrophenyl)-methanesulfonylchloride (3.54 g) and 4-methyl-piperazine (3.6 ml) are reacted together to give 1-Methyl-4-(4-nitro-phenyl-methanesulfonyl)-piperazine melting at 189 - 192°C; Rf (D3) 0.39.

b) 4-(4-methyl-piperazine-1-sulfonylmethyl)-phenylamine

In a procedure analogous to that of Example 45b 1-Methyl-4-(4-nitro-phenylmethane-sulfonyl)-piperazine (4.35 g) is hydrogenated over 5% palladium on carbon (0.8 g) to yield 4-(4-methyl-piperazine-1-sulfonylmethyl)-phenylamine, melting at 136 - 137°C. After addition of 1 equivalent of HCl to a methanolic solution of the free base 4-(4-methyl-piperazine-1-sulfonylmethyl)-phenylamine monohydrochloride is crystallized, melting at 167 - 169°C; Rf (D3) 0.30.

Example 47: N-2-[4-(Morpholine-4-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine hydrochloride

In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.18 g) and 4-(morpholine-4-sulfonylmethyl)-phenylamine (0.19 g) are reacted together to give N-2-[4-(morpholine-4-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine hydrochloride as yellow crystals melting at 268 - 272°C; Rf (A2) 0.22.

The starting material can be prepared, for example, as follows:

a) 4-(4-Nitro-phenylmethanesulfonyl)-morpholine

In a procedure analogous to that of Example 45a (4-nitrophenyl)-methanesulfonylchloride (5.0 g) and morpholine (4.06 g) are reacted together to give 4-(4-nitrophenyl-methanesulfonyl)-morpholine melting at 171 - 172°C; Rf (A2) 0.65.

b) 4-(Morpholine-4-sulfonylmethyl)-phenylamine

In a procedure analogous to that of Example 45b 4-(4-nitro-phenylmethanesulfonyl)-morpholine (5.32 g) is hydrogenated over 5% palladium on carbon (0.5 g) to yield 4-(morpholine-4-sulfonylmethyl)-phenylamine, melting at 166 - 167°C; Rf (A2) 0.47.

Example 48: N,N-Dimethyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (0.32 g) (prepared as described in Example 1a and N,N-dimethyl-[4-amino-phenyl]-methanesulfonamide (0.29 g) (prepared as described in the GB 82-16526) in 5 ml of isopentylalcohol is stirred under nitrogen at 155°C for 10 min in a sealed vessel. The crude product, which is crystallizing on cooling, is filtered off, redissolved in ethylacetate and aqueous sodium carbonate solution and extracted with ethylacetate. The organic extracts are dried and concentrated and the solid residue is titrated with diethylether to give 0.3 g of N,N-dimethyl-[4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide as light yellow crystals melting at 247 - 249°C; Rf (A2) 0.24. Recrystallisation from methanolic HCl and diethylether yields N,N-dimethyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 257 - 260°C.

Example 49: N-(2-Methoxy-ethyl)-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.18 g) and N-(2-methoxy-ethyl)-(4-amino-phenyl)-methanesulfonamide (0.184 g) are reacted together to give N-(2-methoxy-ethyl)-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride of as colorless crystals melting at 266 - 270°C; Rf (A2) 0.18.

The starting material can be prepared, for example, as follows:

a) N-(2-Methoxy-ethyl)-(4-nitro-phenyl)-methanesulfonamide

In a procedure analogous to that of Example 45a (4-nitro-phenyl)-methanesulfonylchloride (5 g) and 2-methoxy-ethylamine (3.5 g) are reacted together to give N-(2-methoxy-ethyl)-(4-nitro-phenyl)-methanesulfonamide melting at 91 - 92°C; Rf (A2) 0.49.

b) N-(2-Methoxy-ethyl)-(4-amino-phenyl)-methanesulfonamide

In a procedure analogous to that of Example 45b N-(2-methoxy-ethyl)-(4-nitro-phenyl)-methanesulfonamide (5 g) is hydrogenated over 5% palladium on carbon to yield N-(2-methoxy-ethyl)-(4-amino-phenyl)-methanesulfonamide melting at 78 - 80°C; Rf (A2) 0.23.

Example 50: 2-[4-(Ethanesulfonylmethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride

In a procedure analogous to that of Example 44 2-chloro-4-phenylamino-quinazoline (0.563 g) and 4-ethanesulfonylmethyl-phenylamine (prepared as described in *I. G. Farbenind. 1934, 623883*) (0.368 g) are reacted together to give 2-[4-(ethanesulfonylmethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride of as colorless crystals melting at 260°C with decomposition; Rf (A2) 0.18, FAB-MS:(M+H)<sup>+</sup> 419.

Example 51: N-{4-[4-(4-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide hydrochloride

A suspension of 2-[4-(aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline (Example 23) (0.41 g) and methanesulfonyl chloride (0.095 ml) in dichloromethane -dioxane (1:1) (10 ml) is stirred at ambient temperature for 16 h. The precipitate is collected by filtration and treated with 4N HCl in dioxane (1 ml) to give N-{4-[4-(4-methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl}-methanesulfonamide hydrochloride, m.p. 275 - 277°C.

The starting material can be prepared, for example, as follows:

a) 2-[4-(Aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride

A solution of 2-(4-cyano-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride (1.00 g) in ethanol (50 ml) is hydrogenated in the presence of Raney nickel (0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is dissolved in methanol and treated with 4N HCl in dioxane (2 ml) and crystallized from isopropanol and diethylether to yield 2-[4-

(aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline dihydrochloride, m.p. 308 - 311°C.

b) 2-(4-Cyano-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

A mixture of 2-chloro-4-(4-methoxy-phenylamino)-quinazoline (1.143 g) and 4-amino-benzonitrile (0.614 g) is heated for 4 min to produce a melt which is dissolved in isopropanol (15 ml). 4N HCl in dioxane (0.1 ml) is added. Crystallization yields 2-(4-cyano-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride, m.p. 340 - 342°C.

Example 52: N-[4-[4-(3-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl]-methanesulfonamide hydrochloride

A suspension of 2-[4-(aminomethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline (Example 23) (0.371 g) and methane-sulfonyl chloride (0.086 ml) in dichloromethane (10 ml) and dioxane (5 ml) is stirred at ambient temperature for 16 h. The precipitate is collected by filtration and is suspended in 2N NaOH. The base is extracted with ethylacetate and treated with 4N HCl in dioxane (1 ml) to give N-[4-[4-(3-methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl]-methanesulfonamide hydrochloride, m.p. 220 - 222°C.

In analogous manner can be prepared:

Example 53: N-[4-(4-Phenylamino-quinazolin-2-ylamino)-benzyl]-methanesulfonamide hydrochloride

M.p. 179 - 181°C.

Example 54: 2-(4-Cyclohexyl-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.38 g) and 4-cyclohexyl-aniline (0.35 g) is heated for 3 min to produce a melt which is dissolved in ethanol (5 ml) and 4 N HCl in dioxane (0.1 ml). Crystallisation from ethanol and diethylether yields 2-(4-cyclohexyl-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 291 - 293°C.

Example 55: 6-Bromo-2,4-di-(3-methoxy-phenylamino)-quinazoline hydrochloride



In a procedure analogous to that of Example 44 6-bromo-2-chloro-4-(3-methoxy-phenylamino)-quinazoline (prepared as described in *Khim.-Farm. Zh.* 1987, 21, 802) (0.278 g) and 3-methoxy-aniline (0.25 ml) are reacted together to give 6-bromo-2,4-di-(3-methoxy-phenylamino)-quinazoline hydrochloride as orange crystals melting at 220 - 228°C; Rf (B1) 0.61.

Example 56: 2-(3-Methoxy-phenylamino)-6-nitro-4-phenylamino-quinazoline hydrochloride

In a procedure analogous to that of Example 44 2-chloro-6-nitro-4-phenylamino-quinazoline (0.527 g) and 3-methoxy-aniline (0.215 ml) are reacted together to give 2-(3-methoxy-phenylamino)-6-nitro-4-phenylamino-quinazoline hydrochloride as brown-orange crystals melting at 247 - 252°C; Rf (A2) 0.55.

The starting material can be prepared, for example, as follows:

2-Chloro-6-nitro-4-phenylamino-quinazoline

In a procedure analogous to that of Example 1a 2,4-dichloro-6-nitro-quinazoline (2.0 g) (prepared as described in JP 78-79950), aniline (0.91 g) (0.184 g) and N,N-diisopropylethylamine (2.1 g) are reacted together to give 2-chloro-6-nitro-4-phenylamino-quinazoline as light yellow crystals melting at 246 - 248°C; Rf (A2) 0.65.

Example 57: 6-Amino-2-(3-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

In a procedure analogous to that of Example 9 2-(3-methoxy-phenylamino)-6-nitro-4-phenylamino-quinazoline hydrochloride (Example 61) (0.435 g) is hydrogenated in the presence of Raney nickel (0.1 g) at ambient temperature and pressure to give 6-amino-2-(3-methoxy-phenylamino)-4-phenylamino-quinazoline dihydrochloride as light-yellow crystals melting at 269 - 273°C; Rf (A1) 0.18.

Example 58: 2,4-Diphenylamino-6-phenyl-quinazoline

A solution of 2,4-dichloro-6-phenyl-quinazoline (0.78 g) and aniline (0.54 ml) in 5 ml of ethanol is stirred under nitrogen at 60°C for 1 h. The crude product, which is crystallizing on cooling, is filtered off, redissolved in ethylacetate and aqueous 1 N NaOH solution and extracted with ethylacetate. The organic extracts are dried, evaporated and the oily residue is chromatographed on silica gel (elution with dichloromethane). Crystallization from methanol yields 2,4-diphenylamino-6-phenyl-quinazoline as colorless crystals melting at 145 - 147°C; Rf (A2) 0.59.

The starting material can be prepared, for example, as follows:

a) 4-Amino-biphenyl-3-carboxylic acid

To a suspension of 2-amino-5-bromo-benzoic acid (10.0 g) in toluene (150 ml) and water (20 ml) is added under an argon atmosphere cesium carbonate (22.0 g), phenylboronic acid (8.2 g) and tetrakis-(triphenylphosphine)-palladium (1.2 g) and the reaction mixture is stirred at reflux temperature for 24 h. The organic layer is separated and washed with 0.1 N aqueous NaOH and water and then decolorized with charcoal and filtered. The colorless filtrate is acidified with aqueous HCl and the precipitate is collected, washed with water and dried to yield 4-amino-biphenyl-3-carboxylic acid as a tan powder melting at 207 - 210°C; Rf (A1) 0.45.

b) 6-Phenyl-quinazolin-2,4-dione

To a suspension of 4-amino-biphenyl-3-carboxylic acid (6.7 g) in dioxane (50 ml), water (30 ml), and acetic acid (3.6 ml) is added a solution of potassium cyanate (6.1 g) in water (20 ml) at 15 - 20°C and the reaction mixture is stirred for 2 h at 25°C. After addition of solid NaOH (7.54 g) the suspension is heated at reflux for 3 h. The reaction mixture is cooled to 0°C, diluted with ice-water (200 ml) and acidified with 2 N HCl. The colorless precipitate is filtered off, washed with ice-water and dried to give 6-phenyl-quinazolin-2,4-dione as a white powder melting at > 300°C; Rf (A1) 0.41.

c) 2,4-Dichloro-6-phenyl-quinazoline

To a suspension of 6-phenyl-quinazolin-2,4-dione (4.5 g) and N,N-dimethylaniline (4.1 ml) in toluene (100 ml) is added slowly phosphorousoxychloride (8.7 ml) and the reaction mixture is heated at reflux for 16 h. The reaction mixture is poured into ice-water, diluted with ethylacetate (200 ml) and the product is extracted with ethylacetate. The organic

extracts are washed with water and 5% aqueous sodium bicarbonate solution, dried and evaporated. The residue is crystallized from diethylether to yield 2,4-dichloro-4-phenyl-quinazoline, m.p. 142 - 144°C; Rf (B2) 0.59.

**Example 59: N,N-Dimethyl-[4-(6-phenyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride**

In a procedure analogous to that of Example 44 2-chloro-6-phenyl-4-phenylamino-quinazoline (0.177 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.125 g) are reacted together to give N,N-dimethyl-[4-(6-phenyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as yellow crystals melting at 258 - 263°C; Rf (A2) 0.40.

**Example 60: N,N-Dimethyl-[4-(5-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride**

A solution of 2-chloro-5-methoxy-4-phenylamino-quinazoline (0.17 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.14 g) in 3 ml of isopentylalcohol is stirred under nitrogen at 160°C for 5 min in a sealed vessel. The warm reaction mixture is diluted with 10 ml ethanol and the hydrochloride salt, which is crystallizing on cooling, is filtered off to yield N,N-dimethyl-[4-(5-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 233 - 236°C; Rf (A2) 0.21.

The starting material can be prepared, for example, as follows:

**2-Chloro-5-methoxy-4-phenylamino-quinazoline**

To a suspension of 2,4-dichloro-5-methoxy-quinazoline (1 g) (prepared as described in *J. Chem. Soc.* **1948**, 1759), N,N-diisopropyl-ethylamine (5.0 ml) and isopropanol (10 ml) is added aniline (0.48 g) and the reaction mixture is heated at 70°C for 0.5 h. The product which is crystallizing on cooling, is filtered off and recrystallized from ethanol to yield 2-chloro-5-methoxy-4-phenylamino-quinazoline as light yellow crystals melting at 191 - 192°C; Rf (B2) 0.12.

**Example 61: N-Methyl-[4-(6-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride**

A solution of 2-chloro-6-methoxy-4-phenylamino-quinazoline (1.15 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (0.89 g) in 5 ml of isopentylalcohol is stirred under nitrogen at 180°C for 20 min in a sealed vessel. The warm reaction mixture is diluted with methanol and the hydrochloride salt, which is crystallizing on cooling, is filtered off. The crude product is redissolved in ethylacetate and aqueous sodium carbonate solution and extracted with ethylacetate. The organic extracts are dried and evaporated and the solid residue is titrated with diethylether to give N-methyl-[4-(6-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide as light yellow crystals melting at 212 - 215°C; (Rf (A2) 0.16. Recrystallisation from methanolic hydrogen chloride and diethylether yields N-methyl-[4-(6-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 264 - 268°C; Rf (A2) 0.16.

The starting material can be prepared, for example, as follows:

**2-Chloro-6-methoxy-4-phenylamino-quinazoline**

In a procedure analogous to that of Example 60 2,4-dichloro-6-methoxy-quinazoline (1.53 g) (prepared as described in *J. Chem. Soc.* 1948, 1759), aniline (0.8 g) (0.184 g) and N,N-diisopropyl-ethylamine (1.72 g) are reacted together to give 2-chloro-6-methoxy-4-phenylamino-quinazoline as light yellow crystals melting at 177 - 179°C; Rf (A2) 0.59.

**Example 62: 6-Methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride**

In a procedure analogous to that of Example 61 2-chloro-6-methoxy-4-phenylamino-quinazoline (0.221 g) and 4-methoxy-aniline (0.114 g) are reacted together to give 6-methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride as light yellow crystals melting at 239 - 242°C; Rf (A2) 0.23.

**Example 63: 2-(4-Hydroxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline hydrochloride**

In a procedure analogous to that of Example 61 2-chloro-6-methoxy-4-phenylamino-quinazoline (0.141 g) and 4-amino-phenol (0.064 g) are reacted together to give 2-(4-hydroxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline hydrochloride as yellow crystals melting at 304 - 308°C; Rf (A2) 0.05.

**Example 64: 2-(4-Benzoyloxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline hydrochloride**

In a procedure analogous to that of Example 61 2-chloro-6-methoxy-4-phenylamino-quinazoline (0.162 g) and 4-benzoyloxyaniline (0.135 g) are reacted together to give 2-(4-benzoyloxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline hydrochloride as brown crystals melting at 269 - 274°C; Rf (A2) 0.22.

**Example 65: N-Methyl-[4-(7-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride**

A solution of 2-chloro-7-methoxy-4-phenylamino-quinazoline (0.105 g) (prepared as described in *J. Chem. Soc.* **1948**, 1759) and N-methyl-[4-amino-phenyl]-methanesulfonamide (0.082 g) in 2 ml of isopentylalcohol is stirred under nitrogen at 170°C for 5 min in a sealed vessel. The warm reaction mixture is diluted with 5 ml ethanol and the hydrochloride salt, which is crystallizing on cooling, is filtered off, to yield N-methyl-[4-(7-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as colorless crystals melting at 273 - 277°C; Rf (A2) 0.11.

**Example 66: N-Methyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride**

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.598 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (prepared as described in *Tetrahedron Letters* **1992**, 33, 8011) (0.540 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (5 ml). Crystallization from isopropanol and diethylether yields N-methyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride, m.p. 289 - 290°C.

The starting material can be prepared, for example, as follows:

2-Chloro-8-methoxy-4-phenylamino-quinazoline

A solution of 2,4-dichloro-8-methoxy-quinazoline (prepared as described in *J. Chem. Soc.* **1948**, 1759) (0.6 g), N,N-diisopropyl-ethylamine (0.87 ml), and aniline (0.26 ml) in isopropanol (10 ml) is heated to reflux for 45 min. The cold reaction mixture is filtered and residue is crystallized from dichloromethane and hexanes to give 2-chloro-8-methoxy-4-phenylamino-quinazoline, m.p. 245 - 246°C.

The following compounds are prepared in an analogous manner:

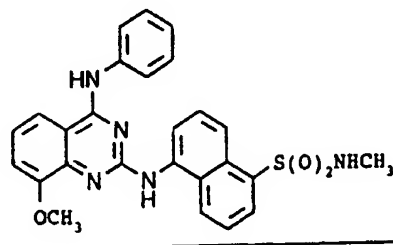
Example 67: N-[4-(8-Methoxy-4-phenylamino-quinazolin-2-ylamino)-benzyl]-methanesulfonamide hydrochloride

Rf(A1) 0.45.

Example 68: N-[4-[8-Methoxy-4-(3-methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl]-methanesulfonamide hydrochloride

Rf(A1) 0.52.

Example 69: 5-[8-Methoxy-4-phenylamino-quinazolin-2-ylamino]-naphthalene-1-sulfonic acid methylamide hydrochloride



A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.427 g) and 5-amino-naphthalene-1-sulfonic acid methylamide (0.424 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (6 ml). Crystallization from isopropanol and diethylether yields 5-[8-methoxy-4-phenylamino-quinazolin-2-ylamino]-naphthalene-1-sulfonic acid methylamide hydrochloride, m.p. 272 - 274°C.

Example 70: 8-Methoxy-2-[4-(piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.2 g) and N-(4-aminophenyl)-piperidine (0.164 g) is heated for 2 min to produce a melt which is dissolved in isopropanol (4 ml). 4N HCl in dioxane (1 ml) is added. Recrystallization from ethanol and diethylether yields 8-methoxy-2-[4-(piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline dihydrochloride, Rf (A1) 0.47.

Example 71: 8-Methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (1.20 g) and 4-methoxy-aniline (0.66 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (15 ml). 4N HCl in dioxane (0.2 ml) is added. Crystallization from isopropanol and diethylether yields 8-methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline dihydrochloride, m.p. 287 - 289°C.

Example 72: 2-(4-Aminomethyl-phenylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride

A solution of 2-(4-cyano-phenylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride (1.10 g) in ethanol (50 ml) is hydrogenated in the presence of Raney nickel (0.5 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is dissolved in methanol. Addition of diethylether yields amorphous 2-(4-aminomethyl-phenylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride, Rf(E1) 0.24.

The starting material can be prepared, for example, as follows:

a) 2-(4-Cyano-phenylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.90 g) and

4-aminobenzonitrile (0.49 g) is heated for 3 min to produce a melt which is dissolved in isopropanol. 4N HCl in dioxane (1.0 ml) is added. Crystallization from isopropanol and diethylether yields 2-(4-cyano-phenylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 307 - 308°C.

b) 2-Chloro-8-methoxy-4-phenylamino-quinazoline

A solution of 2,4-dichloro-8-methoxy-quinazoline (0.60 g), diisopropyl-ethylamine (0.87 ml), and aniline (0.26 ml) in isopropanol (10 ml) is heated to reflux for 45 min. The cold reaction mixture is filtered and residue is crystallized from dichloromethane and hexanes to give 2-chloro-8-methoxy-4-phenylamino-quinazoline, m.p. 245 - 246°C.

c) 2,4-Dichloro-8-methoxy-quinazoline

N,N-Dimethylaniline (0.36 ml) is added slowly to a solution of 8-methoxy-1H,3H-quinazolin-2,4-dione (*J. Chem. Soc.* **1921**,1425) (1.20 g) in phosphorousoxychloride (3.70 ml) while this mixture is heated up to 125°C. After the completion of the addition refluxing is continued for 10 h. Evaporation of the solvent in vacuo gives a residue which is added to ice and water. Extraction with ethylacetate yields 2,4-dichloro-8-methoxy-quinazoline, Rf(C4) 0.64.

Example 73: Naphthalene-1-sulfonic acid 4-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride

A suspension of 0.165 g of 2-chloro-4-amino-quinazoline and 0.3 g of naphthalene-1-sulfonic acid 4-aminomethyl-benzylamide in 16 ml of isopentylalcohol is heated up to 100 °C for 15 hours. The resulting solution is concentrated and chromatographed on silica gel (A1) to give the product as a tan powder. This material is taken up in 7 ml of dichloromethane and treated at 0 °C with 3.5 ml of a 4 N HCl solution in dioxane. Concentration *in vacuo* provides a foam which is triturated in diethylether. The solids are collected and dried to yield naphthalene-1-sulfonic acid 4-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride, melting at 215-224 °C. Rf (A1) 0.35; FAB-MS: (M+H)<sup>+</sup> = 470.

The starting material can be prepared, for example, as follows:



a) {4-[(Naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester

A solution of 3 g of naphthalene-1-sulfonylchloride and 4.53 ml of N,N-diisopropylethylamine in acetonitrile (80 ml) is cooled to 0 °C and treated with a solution of 3.12 g of (4-amino methyl-benzyl)-carbamic acid *tert*-butyl ester (*J. Med. Chem.* 1989, 32, 391-396) in acetonitrile (20 ml). The reaction mixture is stirred at ambient temperature for 30 min and concentrated. The residue is partitioned between dichloromethane and water. The organic phase is dried over magnesium sulfate and concentrated to a tan powder. Chromatography on silica gel (C3 then C2) affords {4-[(naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester melting at 147-149 °C. Rf(C3) 0.25.

b) Naphthalene-1-sulfonic acid 4-aminomethyl-benzylamide

A suspension of {4-[(naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester (5.25 g) in dichloromethane (33 ml) is treated with a 4 N HCl solution in dioxane (33 ml) at 0 °C. Under completion, the reaction mixture is concentrated *in vacuo*, the residue is partitioned between a 1 N aqueous NaOH solution and dichloromethane. After extraction with dichloromethane, the organics are dried over magnesium sulfate and concentrated to yield naphthalene-1-sulfonic acid 4-aminomethyl-benzylamide as a white foam. Rf(C4) 0.42.

Example 74: Naphthalene-1-sulfonic acid 3-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride

In a procedure analogous to that of Example 73, a mixture of 0.264 g 2-chloro-4-amino-quinazoline and 0.48 g of naphthalene-1-sulfonic acid 3-aminomethyl-benzylamide is converted to naphthalene-1-sulfonic acid 3-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride melting at 142-149 °C. Rf(A1) 0.33; FAB-MS: (M+H)<sup>+</sup> = 470.

The starting material can be prepared, for example, as follows:

a) {3-[(Naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester

In a procedure analogous to that of Example 73a, a mixture of 3.12 g of (3-amino methyl-benzyl)-carbamic acid *tert*-butyl ester (*J. Med. Chem.* 1989, 32, 391-396) and 3 g of

naphthalene-1-sulfonylchloride in acetonitrile gives {3-[(naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester melting at 104-105 °C. Rf(C3) 0.41.

**b) Naphthalene-1-sulfonic acid 3-aminomethyl-benzylamide**

Following the procedure described in Example 73b, {3-[(naphthalene-1-sulfonylamino)-methyl]-benzyl}-carbamic acid *tert*-butyl ester (4.97 g) is converted to naphthalene-1-sulfonic acid 3-aminomethyl-benzylamide as a foam. Rf(A3) 0.50.

**Example 75:** In a manner analogous to that described hereinbefore it is also possible to manufacture the following compounds:

2-(N-Methyl-4-methoxy-phenylamino)-8-methoxy-4-(4-cyano-phenylamino)-quinazoline

2-[N<sup>1</sup>-Methyl-4-(acetaminomethyl)-phenylamino]-8-methoxy-4-(4-cyano-phenylamino)-quinazoline

2-[N<sup>1</sup>-Methyl-4-(pyrrolidin-1-yl-methyl)-phenylamino]-4-phenylamino-quinazoline

2-[N<sup>1</sup>-Methyl-4-(pyrrolidin-1-yl-methyl)-phenylamino]-8-methoxy-4-(4-cyano-phenylamino)-quinazoline

4-(4-Chloro-phenylamino)-2-[(4-pyrrolidin-1-yl-methyl)-phenylamino]-8-(2-hydroxy-ethoxy)-quinazoline

1-[4-[4-(4-Chloro-phenylamino)-8-(2-hydroxy-ethoxy)-quinazolin-2-ylamino]-benzyl]-2-pyrrolidin-2-on

2-(2-Chloro-4-methoxy-phenylamino)-8-(2-morpholino-ethoxy)-4-(2-methyl-phenylamino)-quinazoline

2-(2-Chloro-4-methoxy-phenylamino)-4-(2-methyl-phenylamino)-8-methoxy-quinazoline

2-(2-Methyl-4-methoxy-phenylamino)-4-(2-methyl-phenylamino)-8-methoxy-quinazoline

2-(2-Methyl-4-methoxy-phenylamino)-8-(2-morpholino-ethoxy)-4-(2-methyl-phenylamino)-quinazoline

4-(4-Chloro-phenylamino)-2-{4-[(cyclopropylmethyl-methylamino)-methyl]-2-methyl-phenylamino}-8-methoxy-quinazoline

2-[4-(Acetyl-amino-methyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline

2-[4-(Acetyl-amino-methyl)-phenylamino]-8-methoxy-4-(4-methoxy-phenylamino)-quinazoline

{3-[4-(4-Chloro-phenylamino)-8-ethyl-quinazolin-2-ylamino]-benzyl}-benzamide

2-[3-(Acetyl-amino-methyl)-phenylamino]-8-methoxy-4-(3-methoxy-phenylamino)-quinazoline

2-[4-(N-Piperidiny-methyl)-phenylamino]-8-methoxy-4-(4-methoxy-phenylamino)-quinazoline

2-{3-[4-(4-Chloro-phenylamino)-8-(2-methoxy-ethoxy)-quinazolin-2-ylamino]-phenoxy}-N,N-dimethyl-acetamide

4-{4-[4-(4-Chloro-phenylamino)-8-(2-hydroxy-ethoxy)-quinazolin-2-ylamino]-phenyl}-1,1,1-trifluoro-butan-2-one

4-(4-Chloro-phenylamino)-8-methoxy-2-[4-(propane-2-sulfonylmethyl)-phenylamino]-quinazoline

6-N,N-Dimethylamino-4-(4-chloro-phenylamino)-2-[2-methoxymethyl-4-(propane-2-sulfonylmethyl)-phenylamino]-quinazoline

2-[2-Methoxymethyl-4-(propane-2-sulfonylmethyl)-phenylamino]-8-methyl-4-phenylamino-quinazoline

{4-(6-Chloro-4-phenylamino-quinazolin-2-ylamino)-3-methoxymethyl-phenyl}-N,N-dimethyl-methanesulfonamide

{4-[4-(4-Fluoro-phenylamino)-8-(2-hydroxy-ethoxy)-quinazolin-2-ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide

{3-[4-(4-Fluoro-phenylamino)-8-methyl-quinazolin-2-ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide

2-{4-[8-(2-Dimethylamino-ethoxy)-4-(4-fluoro-phenylamino)-quinazolin-2-ylamino]-phenyl}-ethanesulfonic acid dimethylamide

4-(4-Chloro-phenylamino)-2-[2-methoxy-4-(propane-2-sulfonylmethyl)-benzylamino]-6-methyl-quinazoline.

Example 76: N-Methyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride

In a procedure analogous to that of Example 44 2-chloro-8-methyl-4-phenylamino-quinazoline (0.254 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (0.200 g) are reacted together to give N-methyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 307-312°C.

The starting material can be prepared, for example, as follows:

2-Chloro-8-methyl-4-phenylamino-quinazoline

In a procedure analogous to that of Example 60 2,4-dichloro-8-methyl-quinazoline (1.09 g) (prepared as described in *Berichte* 1907, 40, 4414), aniline (0.57 g) and N,N-diisopropyl-

ethylamine (1.31 g) are reacted together to give 2-chloro-8-methyl-4-phenylamino-quinazoline as light yellow crystals melting at 133 - 135°C; Rf (B2) 0.36.

**Example 76: N,N-Dimethyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride**

In a procedure analogous to that of Example 44 2-chloro-8-methyl-4-phenylamino-quinazoline (0.211 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.184 g) are reacted together to give N,N-dimethyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 271 - 275°C.

**Example 77: N,N-Dimethyl-[4-(8-methyl-4-methylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride**

In a procedure analogous to that of Example 44 2-chloro-8-methyl-4-methylamino-quinazoline (0.17 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.179 g) are reacted together to give N,N-dimethyl-[4-(8-methyl-4-methylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 286 - 290°C; Rf (A1) 0.35.

The starting material can be prepared, for example, as follows:

**2-Chloro-8-methyl-4-methylamino-quinazoline**

A solution of 2,4-dichloro-8-methyl-quinazoline (0.336 g) (prepared as described in *Berichte* 1907, 40, 4414) and 5 ml of a 33 % solution of methylamine in ethanol is heated to 80°C for 30 min. in a sealed tube. After evaporation the residue is triturated with water, filtered and dried to give 2-chloro-8-methyl-4-methylamino-quinazoline as colorless crystals melting at 171 - 173°C; Rf (A2) 0.64.

**Example 78: N,N-Dimethyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride**

In a procedure analogous to that of Example 44 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.4 g) (Example 66) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.329 g) are reacted together to give N,N-dimethyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide hydrochloride as light yellow crystals melting at 278 - 281°C; Rf (A1) 0.52.

**Example 79: N(6),N(6)-Dimethyl-N(2),N(4)-diphenyl-quinazoline-2,4,6-triamine hydrochloride**

In a procedure analogous to that of Example 44 (2,4-dichloro-quinazolin-6-yl)-dimethylamine (0.13 g) and aniline (0.11 g) are reacted together to give N(6),N(6)-dimethyl-N(2),N(4)-diphenyl-quinazoline-2,4,6-triamine hydrochloride as yellow crystals melting at 281 - 286°C; Rf (A2) 0.21.

The starting material can be prepared, for example, as follows:

**a) 2-Amino-5-dimethylamino-benzoic acid**

A solution of 5-dimethylamino-2-nitro-benzoic acid (10 g) (prepared as described in *J. Med. Chem.* 1981, 24, 742) in methanol (300 ml) is hydrogenated in the presence of palladium on charcoal 10 % (0.5 g) at atmospheric pressure. The catalyst is removed by filtration through Celite after addition of 2N NaOH (5 ml). The filtrate neutralized with 2N HCl and the precipitate is collected, washed with methanol and dried to yield 2-amino-5-dimethylamino-benzoic acid as brown crystals melting at 224 - 228°C.

**b) 6-Dimethylamino-quinazolin-2,4-dione**

In a procedure analogous to that of Example 58b 2-amino-5-dimethylamino-benzoic acid (5.0 g) and potassium cyanate are reacted to give 6-dimethylamino-quinazolin-2,4-dione as yellow crystals melting at 326 - 329°C.

**c) (2,4-Dichloro-quinazolin-6-yl)-dimethylamine**

To a suspension of 6-dimethyl-quinazolin-2,4-dione (14.5 g) and N,N-dimethylaniline (15.5 g) is added slowly phosphorousoxychloride (66.7 g) and the reaction mixture is heated at reflux for 6 h. The reaction mixture is diluted with toluene (200 ml), poured into ice-water and the product is extracted with toluene. The organic extracts are washed with water, dried

and evaporated. The residue is crystallized from toluene to yield (2,4-dichloro-quinazolin-6-yl)-dimethylamine, m.p. 174 - 176°C; Rf (A2) 0.90.

**Example 80: N(4)-(3-Chlorophenyl)-N(6),N(6)-dimethyl-N(2)-phenyl-quinazoline-2,4,6-triamine hydrochloride**

In a procedure analogous to that of Example 44 2-chloro-N(4)-(3-chlorophenyl)-N(6),N(6)-dimethyl-quinazoline-4,6-diamine (0.092 g) and aniline (0.03 g) are reacted together to give N(4)-(3-chlorophenyl)-N(6),N(6)-dimethyl-N(2)-phenyl-quinazoline-2,4,6-triamine hydrochloride as yellow crystals melting at 299 - 303°C; Rf (A2) 0.26.

The starting material can be prepared, for example, as follows:

**2-Chloro-N(4)-(3-chlorophenyl)-N(6),N(6)-dimethyl-quinazoline-4,6-diamine**

In a procedure analogous to that of Example 60 (2,4-dichloro-quinazolin-6-yl)-dimethylamine (2 g), 3-chloroaniline (1.57 g), N,N-diisopropyl-ethylamine (2.13 g) are reacted together to give 2-chloro-N(4)-(3-chlorophenyl)-N(6),N(6)-dimethyl-quinazoline-4,6-diamine as yellow crystals melting at 199 - 201°C; Rf (A2) 0.70.

**Example 81: [4-(6-Dimethylamino-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide hydrochloride**

In a procedure analogous to that of Example 44 2-chloro-N(6),N(6)-dimethylamino-N(4)-phenyl-quinazoline-4,6-diamine (0.105 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.085 g) are reacted together to give [4-(6-dimethylamino-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide hydrochloride as light yellow crystals melting at 265 - 270°C; Rf (A2) 0.17.

The starting material can be prepared, for example, as follows:

**2-Chloro-N(6),N(6)-dimethylamino-N(4)-phenyl-quinazoline-4,6-diamine**

In a procedure analogous to that of Example 60 (2,4-dichloro-quinazolin-6-yl)-dimethylamine (2 g), aniline (1.15 g), N,N-diisopropyl-ethylamine (5 ml) are reacted together

to give 2-chloro-N(6),N(6)-dimethylamino-N(4)-phenyl-quinazoline-4,6-diamine as yellow crystals melting at 174 - 176°C; Rf (A2) 0.90.

**Example 82: [4-(8-Dimethylaminomethyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide hydrochloride**

In a procedure analogous to that of Example 44 (2-chloro-8-dimethylaminomethyl-quinazolin-4-yl)-phenyl-amine (0.03 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (0.033 g) are reacted together to give [4-(8-dimethylaminomethyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide hydrochloride as light yellow powder; Rf (A1) 0.04.

The starting material can be prepared, for example, as follows:

**a) 8-Bromomethyl-2,4-dichloro-quinazoline**

A solution of 2,4-dichloro-8-methyl-quinazoline (35.5 g) (prepared as described in *Berichte* 1907, 40, 4414), N-bromosuccinimide (35.2 g) and dibenzoylperoxide (0.5 g) in carbon tetrachloride (900 ml) is heated at reflux for 2 h. The reaction mixture is filtered and the filtrate is washed with 0.5 N HCl and aqueous sodium thiosulfate solution. The organic extracts are dried over magnesium sulfate and concentrated. The crude product is recrystallized from isopropanol to give 8-bromomethyl-2,4-dichloro-quinazoline as light yellow needles melting at 160 - 162°C; Rf (B3) 0.19; Rf (B4) 0.43.

**b) 8-Bromomethyl-2-chloro-4-phenylamino-quinazoline**

A solution of 8-bromomethyl-2,4-dichloro-quinazoline (0.552 g), aniline hydrochloride (0.486 g), N,N-diisopropyl-ethylamine (0.64 ml), and N,N-dimethylformamide (10 ml) are reacted together at 25°C for 30 min. The reaction mixture is partitioned between toluene and water. The organic extracts are washed with 0.1 N aqueous HCl solution and brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (toluene) and recrystallization from dichloromethane and hexane yields 8-bromomethyl-2-chloro-4-phenylamino-quinazoline as light yellow crystals melting at 154 - 155°C; Rf (B4) 0.10.

**c) (2-Chloro-8-dimethylaminomethyl-quinazolin-4-yl)-phenyl-amine**

A solution of 8-bromomethyl-2-chloro-4-phenylamino-quinazoline (0.12 g), 0.35 ml of a solution of 8 % dimethylamine in toluene, and N,N-diisopropyl-ethylamine (0.12 ml) are reacted together at 25°C for 3 h. The reaction mixture is partitioned between ethyl acetate and 10 % aqueous sodium carbonate solution. The organic extracts are washed with brine, dried over magnesium sulfate and concentrated. Recrystallization from dichloromethane and hexane gives (2-chloro-8-dimethylaminomethyl-quinazolin-4-yl)-phenyl-amine as light yellow crystals melting at 195 - 197°C; Rf (A2) 0.05.

Example 83: 8-Methoxymethyl-N(2)-(4-methoxy-phenyl)-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride

In a procedure analogous to that of Example 44 (2-chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine (0.09 g) and p-anisidine (0.044 g) are reacted together to give 8-methoxymethyl-N(2)-(4-methoxy-phenyl)-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride as light yellow crystals melting at 252 - 256°C; Rf (A2) 0.48.

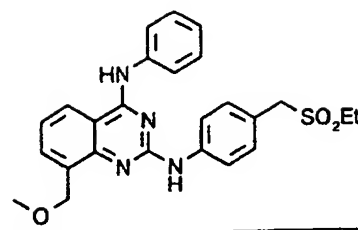
The starting material can be prepared, for example, as follows:

(2-Chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine

To a solution of 8-bromomethyl-2-chloro-4-phenylamino-quinazoline (0.345 g in methanol (30 ml) is added at 40°C a solution of 3 % sodium methylate in methanol (3.74 ml) and the reaction mixture is stirred for 30 min at this temperature. Under completion, the reaction mixture is concentrated *in vacuo*, the residue is partitioned between ethyl acetate and water. The organic extracts are washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (toluene) and recrystallization from diethylether and hexane yields (2-chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine as light yellow crystals melting at 143 - 144°C; Rf (B2) 0.20.

Example 84: N(2)-(4-Ethanesulfonylmethyl-phenyl)-8-methoxymethyl-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride





In a procedure analogous to that of Example 44 (2-chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine (0.205 g) and 4-ethanesulfonylmethyl-phenylamine (prepared as described in *I.G. Farbenind.* 1934, 623 883) (0.156 g) are reacted together to give N(2)-(4-ethanesulfonylmethyl-phenyl)-8-methoxymethyl-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride as yellow crystals melting at 266 - 271°C; Rf (A2) 0.60.

**Example 85: [4-(8-Methoxymethyl-4-phenylamino-quinazolin-2-ylamino-phenyl)]-N-methyl-methanesulfonamide hydrochloride**

In a procedure analogous to that of Example 44 (2-chloro-8-methoxymethyl-quinazolin-4-yl)-phenyl-amine (0.181 g) and N-methyl-(4-aminophenyl)-methanesulfonamide (0.145 g) are reacted together to give [4-(8-methoxymethyl-4-phenylamino-quinazolin-2-ylamino-phenyl)]-N-methyl-methanesulfonamide hydrochloride as yellow crystals melting at 257 - 262°C; Rf (A2) 0.42.

**Example 86: N(2)-(4-Ethanesulfonylmethyl-phenyl)-8-methoxy-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride**

In a procedure analogous to that of Example 44 (2-chloro-8-methoxy-quinazolin-4-yl)-phenyl-amine (example 66) (2.86 g) and 4-ethanesulfonylmethyl-phenylamine (prepared as described in *I.G. Farbenind.* 1934, 623 883) (2.00 g) are reacted together to give N(2)-(4-ethanesulfonylmethyl-phenyl)-8-methoxy-N(4)-phenyl-quinazoline-2,4-diamine hydrochloride as yellow crystals melting at >280°C; Rf (D3) 0.47.

**Example 87: N(4)-Cyclopropyl-N(2)-(4-ethanesulfonylmethyl-phenyl)-8-methoxy-quinazoline-2,4-diamine hydrochloride**

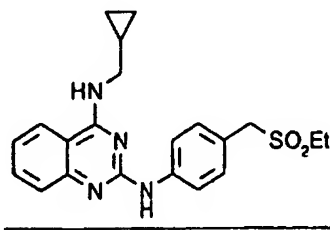
In a procedure analogous to that of Example 44 (2-chloro-8-methoxy-quinazolin-4-yl)--cyclopropyl-amine (0.375 g) and 4-ethanesulfonylmethyl-phenylamine (0.299 g) are reacted together to give N(4)-cyclopropyl-N(2)-(4-ethanesulfonylmethyl-phenyl)-8-methoxy-quinazoline-2,4-diamine hydrochloride as colorless crystals melting at 268 - 270°C; Rf (D1) 0.40.

The starting material can be prepared, for example, as follows:

(2-Chloro-8-methoxy-quinazolin-4-yl)-cyclopropyl-amine

To a solution of 2,4-dichloro-quinazoline (10 g) (Example 1b) in isopropanol (200 ml) is added cyclopropylamine (4.51 g) at 0°C. The reaction mixture is stirred for 1.5 h at room temperature, concentrated *in vacuo*, and the residue is partitioned between chloroform and 0.1 N NaOH. The organic extracts are washed with brine, dried over magnesium sulfate and concentrated. Recrystallization from dichloromethane and hexane yields (2-chloro-8-methoxy-quinazolin-4-yl)-cyclopropyl-amine as white crystals melting at 189 - 191°C; Rf (A2) 0.50.

Example 88: N(4)-Cyclopropylmethylamino-N(2)-(4-ethanesulfonylmethyl-phenylamino)-quinazoline hydrochloride



In a procedure analogous to that of Example 44 2-chloro-4-cyclopropylmethylamino--quinazoline (0.351 g) and 4-ethanesulfonylmethyl-phenylamine (0.299 g) are reacted together to give N(4)-cyclopropylmethylamino-N(2)-(4-ethanesulfonylmethyl-phenylamino)-quinazoline hydrochloride as colorless crystals melting at > 280°C; Rf (D3) 0.45.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-cyclopropylmethyl-amine

In a procedure analogous to that of Example 1a 2,4-dichloro-quinazoline (13 g), cyclopropylamine (5.9 ml), N,N-diisopropyl-ethylamine (13 ml) are reacted together to give (2-chloro-quinazolin-4-yl)-cyclopropylmethyl-amine as light yellow crystals melting at 154 - 155°C; Rf (B1) 0.48.

Example 90: N(2)-(4-Ethansulfonylmethyl-phenyl)-N(4)-methyl-quinazoline-2,4-diamine hydrochloride

In a procedure analogous to that of Example 44 (2-chloro-quinazolin-4-yl)-methyl-amine (0.291 g) and 4-ethanesulfonylmethyl-phenylamine (0.299 g) are reacted together to give N(2)-(4-ethansulfonylmethyl-phenyl)-N(4)-methyl-quinazoline-2,4-diamine hydrochloride as colorless crystals melting at > 280°C; Rf (D3) 0.41.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-methyl-amine

In a procedure analogous to that of Example 1a 2,4-dichloro-quinazoline (15 g) and 8N methylamine in ethanol (20.0 ml) are reacted together to give (2-chloro-quinazolin-4-yl)-methyl-amine as light yellow crystals melting at 212 - 213°C; Rf (B1) 0.33.

Example 91: N(4)-(2-Dimethylamino-ethyl)-N(2)-(4-ethanesulfonylmethyl-phenyl)-quinazoline-2,4-diamine hydrochloride

In a procedure analogous to that of Example 44 N-(2-chloro-quinazolin-4-yl)-N',N'-dimethylethane-1,2-diamine (0.431 g) and 4-ethanesulfonylmethyl-phenylamine (0.299 g) are reacted together to give N(4)-(2-dimethylamino-ethyl)-N(2)-(4-ethanesulfonylmethyl-phenyl)-quinazoline-2,4-diamine hydrochloride as colorless crystals melting at > 240°C; Rf (D3) 0.21.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine

In a procedure analogous to that of Example 1a 2,4-dichloro-quinazoline (5 g) and 2-dimethylamino-ethylamine (2.43 g) are reacted together to give N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine as white crystals melting at 64 - 67°C; Rf (A1) 0.30.

**Example 92: {4-[4-(3-Chlorophenylamino)-quinazolin-2ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide hydrochloride**

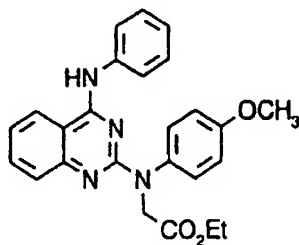
In a procedure analogous to that of Example 44 (3-chlorophenyl)-2-chloro-quinazolin-4-yl-amine (0.29 g) and N,N-dimethyl-(4-aminophenyl)-methanesulfonamide (0.214 g) are reacted together to give {4-[4-(3-chlorophenylamino)-quinazolin-2ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide hydrochloride as colorless crystals melting at 239 - 242°C; Rf (D3) 0.48.

The starting material can be prepared, for example, as follows:

**(3-Chlorophenyl)-2-chloro-quinazolin-4-yl-amine**

In a procedure analogous to that of Example 1a 2,4-dichloro-quinazoline (8.4 g), 3-chloroaniline (4.7 ml), N,N-diisopropyl-ethylamine (15 ml) are reacted together to give (3-chlorophenyl)-2-chloro-quinazolin-4-yl-amine as light yellow crystals melting at 197 - 199°C; Rf (D3) 0.50.

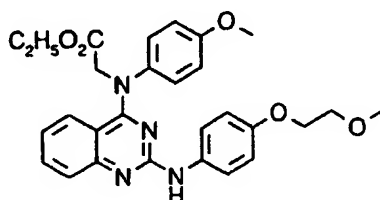
**Example 93: [(4-Methoxyphenyl)-(4-phenylamino-quinazolin-2-yl)amino]-acetic acid ethyl ester**



(2-Chloro-quinazolin-4-yl)-phenyl-amine (1 g) and N-(4-methoxyphenyl)-N-acetic acid ethyl ester (1.1 g) are heated up for 2 min to produce a melt. Isopropanol (2 mL) and water are added subsequently, the aqueous phase is adjusted to pH 11 and extracted with dichloromethane. The crude product is purified by flash chromatography on silica gel

(hexane/ethylacetate 6:1 to 4:1) to give a coloured oil which is recrystallized from a (1:3)-mixture of ethanol/hexane by adding methanol at room temperature. The title compound is obtained as a white crystalline powder, m.p. 93 - 95°C.

Example 94: [(2-[4-(2-methoxyethoxy)-phenylamino]-quinazolin-4-yl-(4-methoxyphenyl))-amino]-acetic acid ethyl ester



A mixture of [(2-chloro-quinazolin-4-yl-(4-methoxyphenyl)amino)-acetic acid ethyl ester (0.5 g) and 4-methoxyethoxy-aniline (0.292 g) is heated up for 1 min to produce a foaming melt. Isopropanol (1 ml), and water (10 ml) are subsequently added, the aqueous phase is adjusted to pH 11 and extracted with dichloromethane. The crude product is purified by flash chromatography on silica gel (hexane/ethylacetate 1:1) to give a yellow foam which is recrystallized from ethanol/hexane 4:1. The title compound is obtained as pale yellow solid, m.p. 126 - 128°C.

The starting material can be prepared, for example, as follows:

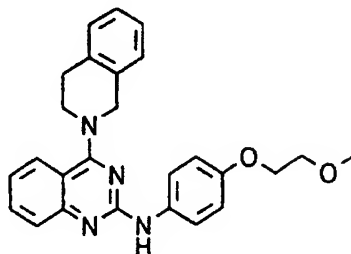
[(2-Chloro-quinazolin-4-yl-(4-methoxyphenyl)amino)-acetic acid ethyl ester

A suspension of 2,4-dichloro-quinazoline (4.5 g), N,N-diisopropyl-ethylamine (9.7 ml) and N-(4-methoxyphenyl)-N-acetic acid ethyl ester (6.15 g) in isopropanol (70 ml) is heated to 80 °C for 20 h. Volatiles are removed by evaporation at reduced pressure, and the residue is partitioned between water and ethylacetate. The combined organics are washed with brine, dried over magnesium sulfate and evaporated. The crude product is purified by flash chromatography on silica gel (hexane/ethylacetate 9:1 to 6:1) to give the title compound as an oil, Rf(C2) 0.33.

Example 95: N(4)-Cyclohexyl-N(4)-ethyl-N(2)-[4-(methoxyethoxy)-phenyl-quinazoline-2,4-diamine hydrochloride

A mixture of 2-chloro-4-[(N-cyclohexyl-N-ethyl)-amino]-quinazoline (0.3 g) and 4-methoxyethoxy-aniline (0.225 g) is heated for 1 min to produce a melt which is dissolved in isopropanol (1 ml). The mixture is evaporated, and the residue is partitioned between dichloromethane (20 ml) and water. The aqueous phase is adjusted to pH 12 and extracted with methylenechloride, the combined organics are dried over magnesium sulfate and evaporated. The crude product is purified by flash chromatography on silica gel (hexane/ethylacetate 1:1) to give a foamy solid. The product is dissolved in dioxane (4 ml), 4N HCl in dioxane (0.268 ml) is added and the mixture is evaporated. The solid material is suspended in diethyl ether and filtered, followed by repeated washing with diethyl ether to yield N(4)-cyclohexyl-N(4)-ethyl-N(2)-[4-(methoxyethoxy)-phenyl]-quinazoline-2,4-diamine hydrochloride as amorphous solid, Rf(A1) 0.48.

Example 96: [4-(3,4-Dihydro-1H-isoquinolin-2-yl)-quinazolin-2-yl]-[4-(2-methoxyethoxy)phenyl]amine hydrochloride



A mixture of 2-chloro-4-(3,4-dihydro-1H-isoquinolin-2-yl)-quinazoline (0.3 g) and 4-methoxyethoxy-aniline (0.657 g) is heated for 1.5 min to produce a melt. Isopropanol (1 ml) and, after cooling, diethyl ether are added. The suspension is filtered, and the pale yellow solid is washed with a (1:1)-mixture of diethyl ether/isopropanol to give [4-(3,4-dihydro-1H-isoquinolin-2-yl)-quinazolin-2-yl]-[4-(2-methoxyethoxy)-phenyl]-amine hydrochloride, Rf(A2) 0.40.

The starting material can be prepared, for example, as follows:

a) 2-Chloro-4-(3,4-dihydro-1H-isoquinolin-2-yl)-quinazoline

A mixture of 2,4-dichloro-quinazoline (4.0 g), N,N-diisopropyl-ethylamine (10.3 ml) and 1,2,3,4-tetrahydroisoquinoline (2.69 ml) in isopentyl alcohol (40 ml) is heated to 150 °C for 2 h. Volatiles are removed by evaporation at reduced pressure, and the residue is partitioned

between a saturated sodium hydrogencarbonate solution and ethylacetate. The combined organics are dried over magnesium sulfate and evaporated. The crude product is purified by flash chromatography on silica gel (hexane/ethylacetate 9:1) to yield 2-chloro-4-(3,4-dihydro-1H-isoquinolin-2-yl)-quinazoline as a pale yellow oil which slowly crystallizes upon standing at room temperature, R<sub>f</sub> (hexane/ethylacetate 6:1) 0.30.

In analogous manner as described hereinbefore, for example, following compounds can be prepared:

Example 97: 2-[4-(Benzoylamino-methyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 228 - 229°C.

Example 98: 2-[4-(Amino-carbonyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 334 - 337°C.

Example 99: 2-[4-(2-Hydroxy-ethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 288 - 291°C.

Example 100: 2-[4-(2-Hydroxy-ethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 229 - 231°C.

Example 101: 2-[4-(2-Hydroxy-ethyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline hydrochloride

R<sub>f</sub>(A1) 0.50.

Example 102: 2-[4-(2-Methoxy-ethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 234 - 236°C.

Example 103: 2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(4-amino-carbonyl-phenylamino)-quinazoline hydrochloride

M.p. 288 - 290°C.

Example 104: 2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 218 - 220°C.

Example 105: 2-[4-(3-Hydroxy-propyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline hydrochloride

M.p. 250 - 252°C.

Example 106: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 252 - 254°C.

Example 107: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 213 - 214°C.

Example 108: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 256 - 257°C.

Example 109: 2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 284 - 284°C.

Example 110: 2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 244 - 245°C.

Example 111: 2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 245 - 246°C.



Example 112: 2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 253 - 254°C.

Example 113: 2-[4-(3-Ethyl-4-methoxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 269 - 270°C.

Example 114: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-cyclohexylamino-quinazoline hydrochloride

M.p. 226 - 227°C.

Example 115: 4-(4-Chloro-phenylamino)-2-[4-(methoxy-acetyl-amino-methyl)-phenylamino]-8-methoxy-quinazoline hydrochloride

M.p. 265 - 266°C.

Example 116: 4-(4-Fluoro-phenylamino)-8-methoxy-2-[4-(2-hydroxyethyl)-phenylamino]-quinazoline hydrochloride

M.p. 235 - 237°C.

Example 117: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline hydrochloride

M.p. 174 - 175°C.

Example 118: 2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-hydroxy-phenylamino)-quinazoline hydrochloride

M.p. 260 - 262°C.

Example 119: 6-Chloro-4-cyclohexylamino-2-[4-(3-hydroxy-propyl)-phenylamino]-quinazoline hydrochloride

M.p. 248 - 249°C.

Example 120: 6-Chloro-4-cyclohexylamino-2-[4-(2-hydroxy-ethoxy)-phenylamino]-quinazoline hydrochloride

M.p. 239 - 240°C.

Example 121: 2-[4-(3-Ethoxy-propoxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 200 - 202°C.

Example 122: 6-Fluoro-2-[4-(3-hydroxy-propyl)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline hydrochloride

Rf(C4) 0.13

Example 123: 2-[4-(3-Benzoyloxy-propoxy)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 177 - 180°C.

Example 124: 2-[4-(3-Benzoyloxy-propoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 138 - 140°C.

Example 125: 2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 257 - 259°C.

Example 126: 4-Cyclohexylamino-2-[4-(3-benzoyloxy-propoxy)-phenylamino]-quinazoline hydrochloride

M.p. 174 - 176°C.

Example 127: 2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(3-hydroxy-phenylamino)-quinazoline hydrochloride

M.p. 227 - 229°C.

Example 128: 2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline hydrochloride

M.p. 204 - 205°C.

Example 129: 4-Cyclohexylamino-2-[4-(3-hydroxy-propoxy)-phenylamino]-quinazoline hydrochloride

M.p. 227 - 229°C.

Example 130: 4-Cyclohexylamino-2-(4-hydroxy-phenylamino)-quinazoline hydrochloride

M.p. 238 - 240°C.

Example 131: 4-Cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride

M.p. 247 - 248°C.

Example 132: 4-(4-Chloro-phenylamino)-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride

M.p. 268 - 269°C.

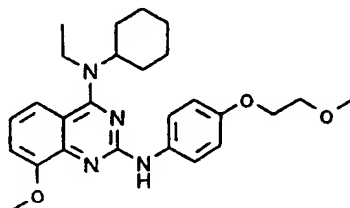
Example 133: 4-(4-Fluoro-phenylamino)-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride

M.p. 257 - 258°C.

Example 134: 4-Cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-quinazoline hydrochloride

M.p. 188 - 190°C.

Example 135: 4-N-Ethyl-cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride



M.p. 267 - 268°C.

Example 136: 4-(4-Chloro-phenylamino)-2-[4-(2-methoxyacetyl-aminomethyl)-phenylamino]-8-methoxy-quinazoline hydrochloride

M.p. 267 - 277°C.

Example 137: 4-Cyclohexylamino-8-methoxy-2-(4-phenylamino)-quinazoline hydrochloride

M.p. 292 - 293°C.

Example 138: 2,4-Di-(4-chloro-phenylamino)-quinazoline hydrochloride

M.p. 360 - 362°C.

Example 139: 2-[4-(2-Methoxyacetyl-aminomethyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline hydrochloride

M.p. 255 - 256°C.

Example 140: 4-Cyclohexylamino-2-[4-(2-hydroxyethyl)-phenylamino]-quinazoline hydrochloride

M.p. 272 - 274°C.

Example 141: 2-[4-Aminomethyl)-phenylamino]-4-(4-chloro-phenylamino)-8-methoxy-quinazoline hydrochloride

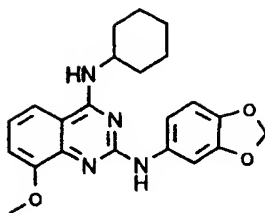
Rf(dichloromethane - methanol-ammonia 40:10:1) 0.10.

Example 142: 2-[4-(3-Hydroxy-propoxy)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline hydrochloride

M.p. 246 - 248°C.

Example 143: 4-Cyclohexylamino-2-[3,4-(methylene-dioxo)-phenylamino]-8-methoxy-quinazoline hydrochloride

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M.p. 290 - 291°C.

Example 144: 2-[3,4-(Methylene-dioxo)-phenylamino]-8-methoxy-4-phenylamino-quinazoline hydrochloride

M.p. 267 - 269°C.

Example 145: 4-(4-Fluoro-phenylamino)-2-[3,4-(methylene-dioxo)-phenylamino]-8-methoxy-quinazoline hydrochloride

M.p. 296 - 297°C.

Example 146: 4-(3-Hydroxy-phenylamino)-2-[4-(piperidin-1-yl)-phenylamino]-quinazoline hydrochloride

Rf(A1) 0.31.

Example 147: 4-(3-Methyl-phenylamino)-2-[4-(3-benzyloxy-propoxy)-phenylamino]-quinazoline hydrochloride

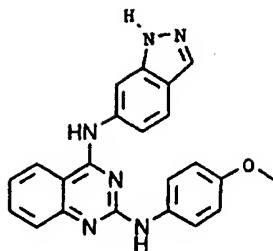
M.p. 138 - 140°C.

Example 148: 2-[4-(2-Acetoxy-ethyl)-phenylamino]-4-phenylamino-quinazoline hydrochloride

M.p. 236 - 238°C.

Example 149: 4-[6-1(H)-Indazol-amino]-2-(4-methoxy-phenylamino)-quinazoline hydrochloride

- 114 -



M.p. 328 - 330°C.

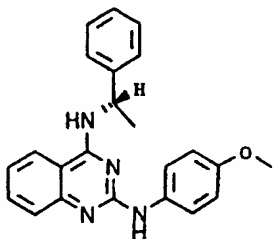
Example 150: 4-Cyclohexylamino-2-[4-(2-acetoxy-ethyl)-phenylamino]-quinazoline hydrochloride

M.p. 228 - 229°C.

Example 151: 4-Cyclohexylamino-2-[4-(3-pivaloyloxy-propoxy)-phenylamino]-quinazoline hydrochloride

M.p. 220 - 221°C.

Example 152: (S)-2-(4-Methoxy-phenylamino)-4-(1-phenyl-ethylamino)-quinazoline hydrochloride



M.p. 269 - 270°C.

Example 153: 4-(4-Chloro-phenylamino)-2-[(2-hydroxy-ethoxy)-phenylamino]-8-methoxy-quinazoline hydrochloride

M.p. 266 - 268°C.

Example 154: 8-Acetoxy-4-(4-chloro-phenylamino)-2-[(2-methoxy-ethoxy)-phenylamino]-quinazoline hydrochloride

R<sub>f</sub> = 0.87 (dichloromethane - methanol 9:1).

Example 155: 4-Cyclohexylamino-2-(4-chloro-3-methoxy-phenylamino)-8-methoxy-quinazoline hydrochloride  
Rf(A1) 0.50.

Example 156: 4-(4-Chloro-3-methoxy-phenylamino)-2-(4-methoxy-phenylamino)-quinazoline hydrochloride  
M.p. 288 - 290°C.

Example 157: Tablets, each containing 50 mg of active ingredient, for example, 2,4-diphenylamino-quinazoline hydrochloride, can be prepared as follows:

Composition (for 10,000 tablets)

Active ingredient	500.0 g
Lactose	500.0 g
Potato starch	352.0 g
Gelatin	8.0 g
Talc	60.0 g
Magnesium stearate	10.0 g
Silica (highly disperse)	20.0 g
Ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch, and the mixture is moistened using an alcoholic solution of the gelatin and granulated by means of a sieve. After drying, the remainder of the potato starch, the talc, the magnesium stearate and the highly disperse silica are admixed and the mixture is compressed to give tablets of weight 145.0 mg each and active ingredient content 50.0 mg which, if desired, can be provided with breaking notches for finer adjustment of the dose.

Example 158: Coated tablets, each containing 100 mg of active ingredient, for example, 2,4-diphenylamino-quinazoline hydrochloride, can be prepared as follows:

Composition (for 1000 tablets):

- 116 -

Active ingredient	100.00 g
Lactose	100.00 g
Corn starch	70.00 g
Talc	8.50 g
Calcium stearate	1.50 g
Hydroxypropylmethylcellulose	2.36 g
Shellac	0.64 g
Water	q.s.
Dichloromethane	q.s.

The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened and granulated with a paste prepared from 15 g of corn starch and water (with warming). The granules are dried, and the remainder of the corn starch, the talc and the calcium stearate are added and mixed with the granules. The mixture is compressed to give tablets (weight: 280 mg) and these are coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of the coated tablet: 283 mg).

Example 159: Tablets and coated tablets containing another compound of the formula (I) or a pharmaceutically acceptable salt of a compound of the formula (I), for example as in one of Examples 1 to 156, can also be prepared in an analogous manner to that described in Examples 157 and 158.



## SEQUENCE LISTING

## (1) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1501 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (iii) HYPOTHETICAL: NO

## (iv) ANTI-SENSE: NO

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 61..1432

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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GAG GAG CAT TTT AAC AAG ACA TTT GTC ACA GAG AAC AAT ACA GCT GCT      156
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- 118 -

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CGC AAT CAG AAG ACT ACA GTG AAC TTT CTC ATA GGC AAC CTG GCC TTC	348
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85 90 95	
TCC GAC ATC TTG GTC GTC CTG TTT TGC TCC CCT TTC ACC CTG ACC TCT	396
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100 105 110	
GTC TTG TTG GAT CAG TGG ATG TTT GGC AAA GCC ATG TGC CAT ATC ATG	444
Val Leu Leu Asp Gln Trp Met Phe Gly Lys Ala Met Cys His Ile Met	
115 120 125	
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145 150 155 160	
AAT TTA ACG GCA AAC CAT GGC TAC TTC CTG ATA GCT ACT GTC TGG ACA	588
Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr	
165 170 175	
CTG GGC TTT GCC ATC TGT TCT CCC CTC CCA GTG TTT CAC AGT CTT GTG	636
Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val	
180 185 190	

- 119 -

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210 215 220	
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225 230 235 240	
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290 295 300	

[illegible]

- 121 -

## (2) INFORMATION FOR SEQ ID NO:2:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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          35             40             45

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          50             55             60

Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Val Met Lys Lys
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Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe
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210 215 220

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275 280 285

Ser Tyr Ser Phe Ile Arg Lys His Arg Arg Arg Tyr Ser Lys Lys Thr  
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Ala Cys Val Leu Pro Ala Pro Ala Gly Pro Ser Gln Gly Lys His Leu  
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Ala Val Pro Glu Asn Pro Ala Ser Val Arg Ser Gln Leu Ser Pro Ser  
325 330 335

Ser Lys Val Ile Pro Gly Val Pro Ile Cys Phe Glu Val Lys Pro Glu  
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Glu Ser Ser Asp Ala His Glu Met Arg Val Lys Arg Ser Ile Thr Arg  
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## (3) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1457 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (iii) HYPOTHETICAL: NO

## (iv) ANTI-SENSE: NO

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 61..1432

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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130 135 140	



ATT	GCC	ATT	GTC	AGG	TAT	CAT	ATG	ATA	AAA	CAT	CCC	ATA	TCT	AAT	AAT	540
Ile	Ala	Ile	Val	Arg	Tyr	His	Met	Ile	Lys	His	Pro	Ile	Ser	Asn	Asn	
145					150					155					160	
TTA	ACA	GCA	AAC	CAT	GGC	TAC	TTT	CTG	ATA	GCT	ACT	GTC	TGG	ACA	CTA	588
Leu	Thr	Ala	Asn	His	Gly	Tyr	Phe	Leu	Ile	Ala	Thr	Val	Trp	Thr	Leu	
				165					170					175		
GGT	TTT	GCC	ATC	TGT	TCT	CCC	CTT	CCA	GTG	TTT	CAC	AGT	CTT	GTG	GAA	636
Gly	Phe	Ala	Ile	Cys	Ser	Pro	Leu	Pro	Val	Phe	His	Ser	Leu	Val	Glu	
			180					185					190			
CTT	CAA	GAA	ACA	TTT	GGT	TCA	GCA	TTG	CTG	AGC	AGC	AGG	TAT	TTA	TGT	684
Leu	Gln	Glu	Thr	Phe	Gly	Ser	Ala	Leu	Leu	Ser	Ser	Arg	Tyr	Leu	Cys	
			195				200					205				
GTT	GAG	TCA	TGG	CCA	TCT	GAT	TCA	TAC	AGA	ATT	GCC	TTT	ACT	ATC	TCT	732
Val	Glu	Ser	Trp	Pro	Ser	Asp	Ser	Tyr	Arg	Ile	Ala	Phe	Thr	Ile	Ser	
	210						215				220					
TTA	TTG	CTA	GTT	CAG	TAT	ATT	CTG	CCC	TTA	GTT	TGT	CTT	ACT	GTA	AGT	780
Leu	Leu	Leu	Val	Gln	Tyr	Ile	Leu	Pro	Leu	Val	Cys	Leu	Thr	Val	Ser	
225					230					235					240	
CAT	ACA	AGT	GTC	TGC	AGA	AGT	ATA	AGC	TGT	GGA	TTG	TCC	AAC	AAA	GAA	828
His	Thr	Ser	Val	Cys	Arg	Ser	Ile	Ser	Cys	Gly	Leu	Ser	Asn	Lys	Glu	
				245					250					255		
AAC	AGA	CTT	GAA	GAA	AAT	GAG	ATG	ATC	AAC	TTA	ACT	CTT	CAT	CCA	TCC	876
Asn	Arg	Leu	Glu	Glu	Asn	Glu	Met	Ile	Asn	Leu	Thr	Leu	His	Pro	Ser	
			260					265					270			
AAA	AAG	AGT	GGG	CCT	CAG	GTG	AAA	CTC	TCT	GGC	AGC	CAT	AAA	TGG	AGT	924
Lys	Lys	Ser	Gly	Pro	Gln	Val	Lys	Leu	Ser	Gly	Ser	His	Lys	Trp	Ser	
		275					280					285				
TAT	TCA	TTC	ATC	AAA	AAA	CAC	AGA	AGA	AGA	TAT	AGC	AAG	AAG	ACA	GCA	972
Tyr	Ser	Phe	Ile	Lys	Lys	His	Arg	Arg	Arg	Tyr	Ser	Lys	Lys	Thr	Ala	
	290					295					300					

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TGT GTG TTA CCT GCT CCA GAA AGA CCT TCT CAA GAG AAC CAC TCC AGA 1020  
Cys Val Leu Pro Ala Pro Glu Arg Pro Ser Gln Glu Asn His Ser Arg  
305 310 315 320

ATA CTT CCA GAA AAC TTT GGC TCT GTA AGA AGT CAG CTC TCT TCA TCC 1068  
Ile Leu Pro Glu Asn Phe Gly Ser Val Arg Ser Gln Leu Ser Ser Ser  
325 330 335

AGT AAG TTC ATA CCA GGG GTC CCC ACT TGC TTT GAG ATA AAA CCT GAA 1116  
Ser Lys Phe Ile Pro Gly Val Pro Thr Cys Phe Glu Ile Lys Pro Glu  
340 345 350

GAA AAT TCA GAT GTT CAT GAA TTG AGA GTA AAA CGT TCT GTT ACA AGA 1164  
Glu Asn Ser Asp Val His Glu Leu Arg Val Lys Arg Ser Val Thr Arg  
355 360 365

ATA AAA AAG AGA TCT CGA AGT GTT TTC TAC AGA CTG ACC ATA CTG ATA 1212  
Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile  
370 375 380

TTA GTA TTT GCT GTT AGT TGG ATG CCA CTA CAC CTT TTC CAT GTG GTA 1260  
Leu Val Phe Ala Val Ser Trp Met Pro Leu His Leu Phe His Val Val  
385 390 395 400

ACT GAT TTT AAT GAC AAT CTT ATT TCA AAT AGG CAT TTC AAG TTG GTG 1308  
Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val  
405 410 415

TAT TGC ATT TGT CAT TTG TTG GGC ATG ATG TCC TGT TGT CTT AAT CCA 1356  
Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro  
420 425 430

ATT CTA TAT GGG TTT CTT AAT AAT GGG ATT AAA GCT GAT TTA GTG TCC 1404  
Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Val Ser  
435 440 445

CTT ATA CAC TGT CTT CAT ATG TAA TAA TTCTCACTGT TTACCAAGGA 1452  
Leu Ile His Cys Leu His Met \* \*  
450 455

**AAGAAC**

1457

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## (4) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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Met Ser Phe Tyr Ser Lys Gln Asp Tyr Asn Met Asp Leu Glu Leu Asp
 1             5             10             15

Glu Tyr Tyr Asn Lys Thr Leu Ala Thr Glu Asn Asn Thr Ala Ala Thr
      20             25             30

Arg Asn Ser Asp Phe Pro Val Trp Asp Asp Tyr Lys Ser Ser Val Asp
      35             40             45

Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu
      50             55             60

Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Leu Met Lys Lys Arg
      65             70             75             80

Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser
      85             90             95

Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val
      100            105            110

Leu Leu Asp Gln Trp Met Phe Gly Lys Val Met Cys His Ile Met Pro
      115            120            125

Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser
      130            135            140

Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn Asn
      145            150            155            160

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Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu  
165 170 175

Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val Glu  
180 185 190

Leu Gln Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Arg Tyr Leu Cys  
195 200 205

Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser  
210 215 220

Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser  
225 230 235 240

His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser Asn Lys Glu  
245 250 255

Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser  
260 265 270

Lys Lys Ser Gly Pro Gln Val Lys Leu Ser Gly Ser His Lys Trp Ser  
275 280 285

Tyr Ser Phe Ile Lys Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala  
290 295 300

Cys Val Leu Pro Ala Pro Glu Arg Pro Ser Gln Glu Asn His Ser Arg  
305 310 315 320

Ile Leu Pro Glu Asn Phe Gly Ser Val Arg Ser Gln Leu Ser Ser Ser  
325 330 335

Ser Lys Phe Ile Pro Gly Val Pro Thr Cys Phe Glu Ile Lys Pro Glu  
340 345 350

Glu Asn Ser Asp Val His Glu Leu Arg Val Lys Arg Ser Val Thr Arg  
355 360 365

Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile  
370 375 380

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Leu Val Phe Ala Val Ser Trp Met Pro Leu His Leu Phe His Val Val  
385                      390                      395                      400

Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val  
                    405                      410                      415

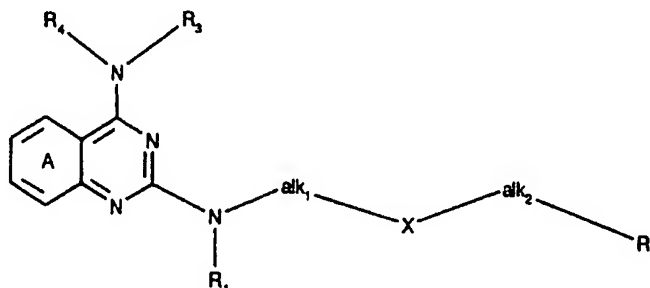
Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro  
                    420                      425                      430

Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Val Ser  
                    435                      440                      445

Leu Ile His Cys Leu His Met \* \*  
450                      455

What is claimed is

1. Use of a compound of formula (I)



in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R<sub>2</sub> represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxy-carbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, by carbamoyl, or by N-substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxy-carbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is di-

substituted by lower alkylene {which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>} or which is disubstituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X<sub>1</sub>(X<sub>2</sub>)(X<sub>3</sub>) wherein, (a) if X<sub>1</sub> is -CH-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>r</sub>-, or -(CH<sub>2</sub>)<sub>s</sub>-X<sub>4</sub>-CO-(CH<sub>2</sub>)<sub>t</sub>-; or, (b) if X<sub>1</sub> is -N-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -CO-(CH<sub>2</sub>)<sub>u</sub>-; [X<sub>4</sub> being -CH<sub>2</sub>-, -N(R<sub>1</sub>)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X<sub>4</sub> is different from -CH<sub>2</sub>-];

R<sub>3</sub> and R<sub>4</sub>, independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or  
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -S(O)<sub>n</sub>-R;

R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, NR<sub>0</sub>] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents (carbocyclic or heterocyclic) arylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO<sub>2</sub>-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy; or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype.

2. Use according to claim 1 for the manufacture of a pharmaceutical composition for treatment and prophylaxis of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dyslipidemia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbance, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.



3. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R<sub>2</sub> represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by lower alkoxy, by substituted amino, by lower alkoxy-carbonyl, or by N-substituted carbamoyl;

(ii) substituted amino;

(iii) hydroxy, lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cyclo-alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxy-carbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X<sub>1</sub>(X<sub>2</sub>)(X<sub>3</sub>) wherein, (a) if X<sub>1</sub> is -CH-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>r</sub>-, or -(CH<sub>2</sub>)<sub>s</sub>-X<sub>4</sub>-CO-(CH<sub>2</sub>)<sub>t</sub>-, or, (b) if X<sub>1</sub> is -N-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -CO-(CH<sub>2</sub>)<sub>u</sub>-, [X<sub>4</sub> being -CH<sub>2</sub>-, -N(R<sub>1</sub>)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X<sub>4</sub> is different from -CH<sub>2</sub>-];

R<sub>3</sub> and R<sub>4</sub>, independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, N-substituted carbamoyl, and  $-S(O)_n-R$ ;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ , or  $NR_0$ ] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene, naphthylene, thiophenylene, furylene, or pyridylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3-C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinoliny, isoquinoliny, or quinazoliny;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

4. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk<sub>1</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

alk<sub>2</sub> represents a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl or lower alkyl which is substituted by lower alkoxy-carbonyl;

R<sub>2</sub> represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, or phenyl;

(ii) amino, amino which is mono-substituted by lower alkyl, by lower alkoxy-lower alkyl, by phenyl, by pyridyl, or which is disubstituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene;

(iii) hydroxy, lower alkanoyloxy, or lower alkoxy which is unsubstituted or substituted by hydroxy, by lower alkoxy, by phenyl-lower alkoxy, by lower-alkanoyloxy, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl or by phenyl;

(iv) a group selected from -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R being lower alkyl, lower alkoxy-lower alkyl, phenyl, or naphthyl, and the group -N(R)(R<sub>1</sub>) represents amino which is mono-substituted by lower alkyl or by lower alkoxy-lower alkyl, or which is di-substituted by lower alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene (which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or lower alkyl)];

(vi) carbamoyl;

$R_3$  represents hydrogen, lower alkyl which is unsubstituted or substituted by  $C_3-C_7$ -cycloalkyl, by phenyl, or by di-lower alkylamino, or represents  $C_3-C_7$ -cycloalkyl, phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, hydroxy, and carbamoyl, or represents indazolyl;

$R_4$  represents hydrogen or lower alkyl which is unsubstituted or substituted by lower alkoxy-carbonyl; or

$R_3$  and  $R_4$  together represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, or oxy-lower alkylene-oxy, or represents naphthylene;

wherein the benzo ring A is unsubstituted or substituted a substituent selected from the group consisting of: halogen, nitro, amino, di-lower alkylamino, lower alkyl, lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkyl, di-(lower alkyl)-amino-lower alkyl, phenyl, and lower alkanoyl.

The invention relates especially to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

$alk_1$  represents a single bond;

$alk_2$  represents a single bond or  $C_1-C_3$ -alkylene;

$R_1$  represents hydrogen or lower alkyl;

$R_2$  represents

(i) hydrogen, halogen, cyano, nitro, lower alkyl, or phenyl;

(ii) amino which is mono-substituted by lower alkyl, phenyl or pyridyl, or which is disubstituted by lower alkyl or by  $C_2-C_6$ -alkylene;

(iii) hydroxy or lower alkoxy which is unsubstituted or substituted by  $C_3-C_8$ -cycloalkyl or by phenyl;

(iv) a group selected from  $-CH(OH)-R$ ,  $-CO-R$ ,  $-NR_1-CO-R$ ,  $-NR_1-SO_2-R$ ,  $-NR_1-SO_2-NR_1-R_1$ ,  $-SO_2-R$ , or  $-SO_2-NR_1-R$ , [R being lower alkyl, halo-lower alkyl, phenyl, pyridyl, or naphthyl,  $R_1$  being as defined above, or the group  $-N(R)(R_1)$  represents amino which is mono-substituted by lower alkyl, by hydroxy-lower alkyl, or by naphthyl, or which is di-substituted by lower alkyl or by  $C_2-C_6$ -alkylene {which may be interrupted by O or  $NR_0$ ,  $R_0$  being hydrogen or lower alkyl}];

R<sub>3</sub> represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, lower alkyl, lower alkoxy, and oxy-lower alkylene-oxy;

R<sub>4</sub> represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, lower alkyl, halo-lower alkyl, lower alkoxy, lower alkoxy-lower alkyl;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, halo-lower alkyl, lower alkoxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

5. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a) alk<sub>1</sub> and alk<sub>2</sub> both represents a single bond; and

R<sub>2</sub> represents hydrogen, amino which is disubstituted by by C<sub>2</sub>-C<sub>6</sub>-alkylene, especially pentylene, or C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially methoxy; or

(b) alk<sub>1</sub> represents a single bond; alk<sub>2</sub> represents C<sub>1</sub>-C<sub>3</sub>-alkylene; and

R<sub>2</sub> represents (iv) a group selected from -NH-SO<sub>2</sub>-R, -SO<sub>2</sub>-R, or -SO<sub>2</sub>-NH-R, [R being C<sub>1</sub>-C<sub>4</sub>-alkyl, or naphthyl, or the group -NH(R) represents amino which is mono-substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl, by hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, or by naphthyl, or which is di-substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl or by C<sub>2</sub>-C<sub>6</sub>-alkylene {which may be interrupted by O or NR<sub>0</sub>, R<sub>0</sub> being hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl}];

and, in each case,

R<sub>1</sub> represents hydrogen;

R<sub>3</sub> represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, and oxy-C<sub>1</sub>-C<sub>4</sub>-alkylene-oxy; and

R<sub>4</sub> represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl, or C<sub>1</sub>-C<sub>4</sub>-alkoxy;

wherein the benzo ring A is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy.

6. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

(a)  $\text{alk}_1$  and  $\text{alk}_2$  both represents a single bond; and

$\text{R}_2$  represents hydrogen, amino which is disubstituted by  $\text{C}_2\text{-C}_6$ -alkylene, especially pentylene, or  $\text{C}_1\text{-C}_4$ -alkoxy, especially methoxy; or

(b)  $\text{alk}_1$  represents a single bond;  $\text{alk}_2$  represents  $\text{C}_1\text{-C}_3$ -alkylene; and

$\text{R}_2$  represents (iv) a group selected from  $-\text{NH-SO}_2\text{-R}$ ,  $-\text{SO}_2\text{-R}$ , or  $-\text{SO}_2\text{-NH-R}$ , [R being  $\text{C}_1\text{-C}_4$ -alkyl, or naphthyl, or the group  $-\text{NH(R)}$  represents amino which is mono-substituted by  $\text{C}_1\text{-C}_4$ -alkyl, by hydroxy- $\text{C}_1\text{-C}_4$ -alkyl, or by naphthyl, or which is di-substituted by  $\text{C}_1\text{-C}_4$ -alkyl or by  $\text{C}_2\text{-C}_6$ -alkylene {which may be interrupted by O or  $\text{NR}_0$ ,  $\text{R}_0$  being hydrogen or  $\text{C}_1\text{-C}_4$ -alkyl}];

and, in each case,

$\text{R}_1$  represents hydrogen;

$\text{R}_3$  represents phenyl which is unsubstituted or is substituted by a substituent selected from the group consisting of: halogen, cyano,  $\text{C}_1\text{-C}_4$ -alkyl,  $\text{C}_1\text{-C}_4$ -alkoxy, and oxy-  $\text{C}_1\text{-C}_4$ -alkylene-oxy; and

$\text{R}_4$  represents hydrogen;

X represents phenylene which is unsubstituted or substituted by halogen,  $\text{C}_1\text{-C}_4$ -alkyl, or  $\text{C}_1\text{-C}_4$ -alkoxy;

wherein the benzo ring A is unsubstituted or substituted by  $\text{C}_1\text{-C}_4$ -alkoxy.

7. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

$\text{alk}_1$  represents a single bond;

$\text{alk}_2$  represents a single bond or  $\text{C}_1\text{-}$  or  $\text{C}_2$ -alkylene;

$\text{R}_1$  represents hydrogen;

$\text{R}_2$  represents hydrogen, hydroxy,  $\text{C}_1\text{-C}_4$ -alkoxy, especially methoxy, lower alkoxy-lower alkoxy, phenyl-lower alkoxy-lower alkoxy, amino, amino which is disubstituted by  $\text{C}_2\text{-C}_6$ -alkylene, especially pentylene, lower alkoxycarbonyl-amino, or  $-\text{SO}_2\text{-R}$  or  $-\text{SO}_2\text{-NH-R}$  and R being  $\text{C}_1\text{-C}_4$ -alkyl, especially methyl; and, in each case;

$\text{R}_3$  represents  $\text{C}_3\text{-C}_6$ -cycloalkyl, phenyl-lower alkyl, or phenyl which is unsubstituted or is substituted by halogen, hydroxy, or lower alkoxy;

$\text{R}_4$  represents hydrogen; and

X represents 1,4-phenylene or 1,3-phenylene which is di-substituted by oxy-methylene-oxy;

wherein the benzo ring A is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially, methoxy, preferably in position 8 of the quinazoline ring.

8. Use according to claim 1 or 2 of a compound of formula (I) or a pharmaceutically acceptable salt thereof in which

alk<sub>1</sub> and alk<sub>2</sub> both represent a single bond;

R<sub>1</sub> is hydrogen;

R<sub>4</sub> is hydrogen;

X is 1,4-phenylene;

R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially methoxy, and R<sub>3</sub> is phenyl which is substituted by hydroxy, especially 3-hydroxy-phenyl; or

R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially 2-methoxy-ethoxy, or 1-piperidino; and

R<sub>3</sub> is phenyl; and

the benzo ring A is unsubstituted or substituted in position 8 of the quinazoline ring by C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially methoxy.

9. A compound of formula (I) or a salt thereof in which;

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R<sub>2</sub> represents a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X<sub>1</sub>(X<sub>2</sub>)(X<sub>3</sub>) wherein, (a) if X<sub>1</sub> is -CH-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-X<sub>4</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>r</sub>-, or -(CH<sub>2</sub>)<sub>s</sub>-X<sub>4</sub>-CO-(CH<sub>2</sub>)<sub>t</sub>-; or, (b) if X<sub>1</sub> is -N-, X<sub>2</sub> together with X<sub>3</sub> represent a structural element of formula -CO-(CH<sub>2</sub>)<sub>u</sub>-; [X<sub>4</sub> being -CH<sub>2</sub>-, -N(R<sub>1</sub>)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X<sub>4</sub> is different from -CH<sub>2</sub>-];

$R_3$  and  $R_4$ , independently of one another, represent

- (i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and  $-S(O)_n-R$ ;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ ,  $NR_0$ ] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

X represents (carbocyclic or heterocyclic) arylene;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

- (i) halogen, lower alkyl, lower alkenyl, lower alkynyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

- (iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3$ - $C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

- (iv) amino, substituted amino;

- (v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;



(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO<sub>2</sub>-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

10. A compound according to claim 9 of formula (I) or a salt thereof selected from the group consisting of

2,4-Diphenylamino-quinazoline,  
2-(4-Methoxy-phenylamino)-4-phenylamino-quinazoline;  
2-(4-Fluoro-phenylamino)-4-phenylamino-quinazoline;  
2-(4-Phenyl-phenylamino)-4-phenylamino-quinazoline;  
2-[4-(N,N-Dimethylamino)-phenylamino]-4-phenylamino-quinazoline;  
2-(3,4-Dimethoxy-phenylamino)-4-phenylamino-quinazoline;  
2-[4-(N,N-Diethylamino)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(Benzyloxy)-phenylamino]-4-phenylamino-quinazoline;  
2-(4-Amino-phenylamino)-4-phenylamino-quinazoline;  
2-[3-(N,N-Dimethylamino)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(N,N-Dipropylamino)-phenylamino]-4-phenylamino-quinazoline;  
2-(4-Cyano-phenylamino)-4-phenylamino-quinazoline;  
2-[4-(2-Pyridylamino)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(Aminomethyl)-phenylamino]-4-phenylamino-quinazoline;  
2-[3-(Aminomethyl)-phenylamino]-4-phenylamino-quinazoline;  
2-(4-Hydroxy-phenylamino)-4-phenylamino-quinazoline;  
2-[4-(3-Cyclohexyl-propyloxy)-phenylamino]-4-phenylamino-quinazoline;  
2,4-Di-(4-methoxy-phenylamino)-quinazoline;  
2-(4-Cyano-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(N,N-Diethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-(4-Cyclohexyl-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline;  
2-(4-Methoxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(Aminomethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-(4-N,N-Diethylamino-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(N,N-Dipropylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
2-(4-Cyclohexyl-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline;  
2-(4-Hydroxy-phenylamino)-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(2-Pyridylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(N,N-Dimethylamino)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(Piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(Benzyloxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-(4-Hydroxy-phenylamino)-4-(3-methoxy-phenylamino)-quinazoline;  
2-[3-(N,N-Dimethylamino)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-(4-Chloro-phenylamino)-4-phenylamino-quinazoline;  
2-(4-Methyl-phenylamino)-4-phenylamino-quinazoline;  
2-(3-Methoxy-phenylamino)-4-phenylamino-quinazoline;  
2-(2-Methoxy-phenylamino)-4-phenylamino-quinazoline;  
2-(4-Nitro-phenylamino)-4-phenylamino-quinazoline;  
2,4-Di-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(Benzyloxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(Aminomethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(Piperidin-1-yl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(Piperidin-1-yl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
N-Methyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;  
N-2-[4-(4-Methyl-piperidine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine;  
N-2-[4-(N-Methyl-piperazine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine;

N-2-[4-(N-Methyl-piperazine-1-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine;  
N-2-[4-(Morpholine-4-sulfonylmethyl)-phenyl]-N-4-phenyl-quinazoline-2,4-diamine;  
N,N-Dimethyl-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;  
N-(2-Methoxy-ethyl)-[4-(4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;  
2-[4-(Ethanesulfonylmethyl)-phenylamino]-4-phenylamino-quinazoline;  
N-[4-[4-(4-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl]-methanesulfonamide;  
N-[4-[4-(4-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl]-methanesulfonamide;  
N-[4-[4-(3-Methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl]-methanesulfonamide;  
N-[4-(4-Phenylamino-quinazolin-2-ylamino)-benzyl]-methanesulfonamide;  
6-Bromo-2,4-di-(3-methoxy-phenylamino)-quinazoline;  
6-Bromo-2,4-di-(3-methoxy-phenylamino)-quinazoline;  
2-(3-Methoxy-phenylamino)-6-nitro-4-phenylamino-quinazoline;  
6-Amino-2-(3-methoxy-phenylamino)-4-phenylamino-quinazoline;  
2,4-Diphenylamino-6-phenyl-quinazoline;  
N,N-Dimethyl-[4-(6-phenyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;  
N,N-Dimethyl-[4-(5-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;  
N-Methyl-[4-(6-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;  
6-Methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline;  
2-(4-Hydroxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline;  
2-(4-Benzoyloxy-phenylamino)-6-methoxy-4-phenylamino-quinazoline;  
N-Methyl-[4-(7-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;  
N-Methyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;  
N-[4-(8-Methoxy-4-phenylamino-quinazolin-2-ylamino)-benzyl]-methanesulfonamide;  
N-[4-[8-Methoxy-4-(3-methoxy-phenylamino)-quinazolin-2-ylamino]-benzyl]-methanesulfonamide;  
5-[8-Methoxy-4-phenylamino-quinazolin-2-ylamino)-naphthalene-1-sulfonic acid methylamide;  
8-Methoxy-2-[4-(piperidin-1-yl)-phenylamino]-4-phenylamino-quinazoline;  
8-Methoxy-2-(4-methoxy-phenylamino)-4-phenylamino-quinazoline;  
2-(4-Aminomethyl-phenylamino)-8-methoxy-4-phenylamino-quinazoline;  
Naphthalene-1-sulfonic acid 4-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide;

Naphthalene-1-sulfonic acid 3-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide;  
N-Methyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methanesulfonamide;  
N,N-Dimethyl-[4-(8-methyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;  
N,N-Dimethyl-[4-(8-methyl-4-methylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;  
N,N-Dimethyl-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-phenyl]-methane-sulfonamide;  
N(6),N(6)-Dimethyl-N(2),N(4)-diphenyl-quinazoline-2,4,6-triamine;  
N(4)-(3-Chlorophenyl)-N(6),N(6)-dimethyl-N(2)-phenyl-quinazoline-2,4,6-triamine;  
[4-(6-Dimethylamino-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methane-sulfonamide;  
[4-(8-Dimethylaminomethyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N,N-dimethyl-methanesulfonamide;  
8-Methoxymethyl-N(2)-(4-methoxy-phenyl)-N(4)-phenyl-quinazoline-2,4-diamine;  
N(2)-(4-Ethanesulfonylmethyl-phenyl)-8-methoxymethyl-N(4)-phenyl-quinazoline-2,4-diamine;  
[4-(8-Methoxymethyl-4-phenylamino-quinazolin-2-ylamino)-phenyl]-N-methyl-methanesulfonamide;  
N(2)-(4-Ethanesulfonylmethyl-phenyl)-8-methoxy-N(4)-phenyl-quinazoline-2,4-diamine;  
N(4)-Cyclopropyl-N(2)-(4-ethanesulfonylmethyl-phenyl)-8-methoxy-quinazoline-2,4-diamine;  
N(4)-Cyclopropylmethylamino-N(2)-(4-ethanesulfonylmethyl-phenylamino)-quinazoline;  
N(2)-(4-Ethanesulfonylmethyl-phenyl)-N(4)-methyl-quinazoline-2,4-diamine;  
N(4)-(2-Dimethylamino-ethyl)-N(2)-(4-ethanesulfonylmethyl-phenyl)-quinazoline-2,4-diamine;  
{4-[4-(3-Chlorophenylamino)-quinazolin-2ylamino]-phenyl}-N,N-dimethyl-methanesulfonamide;  
[(4-Methoxyphenyl)-(4-phenylamino-quinazolin-2-yl)amino]-acetic acid ethyl ester;  
[{2-[4-(2-methoxyethoxy)-phenylamino]-quinazolin-4-yl}-(4-methoxyphenyl)amino]-acetic acid ethyl ester;  
N(4)-Cyclohexyl-N(4)-ethyl-N(2)-[4-(methoxyethoxy)-phenyl-quinazoline-2,4-diamine;  
[4-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-quinazolin-2-yl]-[4-(2-methoxyethoxy)phenyl]amine;  
2-[4-(Benzoylamino-methyl)-phenylamino]-4-phenylamino-quinazoline;

2-[4-(Amino-carbonyl)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(2-Hydroxy-ethyl)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(2-Hydroxy-ethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(2-Hydroxy-ethyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline;  
2-[4-(2-Methoxy-ethyl)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(4-amino-carbonyl-phenylamino)-quinazoline;  
2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(3-Hydroxy-propyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline;  
2-[4-(3-Hydroxy-propyl)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(2-Hydroxy-ethoxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(2-Methoxy-ethyl)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
2-[4-(3-(2-[4-(3-Hydroxy-propyl)-phenylamino]-4-cyclohexylamino)-quinazoline);  
2-[4-(3-Ethyl-4-methoxy)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(3-Hydroxy-propyl)-phenylamino]-4-cyclohexylamino-quinazoline;  
4-(4-Chloro-phenylamino)-2-[4-(methoxy-acetyl-amino-methyl)-phenylamino]-8-methoxy-quinazoline;  
4-(4-Fluoro-phenylamino)-8-methoxy-2-[4-(2-hydroxyethyl)-phenylamino]-quinazoline;  
2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline;  
2-[4-(3-Hydroxy-propyl)-phenylamino]-4-(3-hydroxyl-phenylamino)-quinazoline;  
6-Chloro-4-cyclohexylamino-2-[4-(3-hydroxy-propyl)-phenylamino]-quinazoline;  
6-Chloro-4-cyclohexylamino-2-[4-(2-hydroxy-ethoxy)-phenylamino]-quinazoline;  
2-[4-(3-Ethoxy-propoxy)-phenylamino]-4-phenylamino-quinazoline;  
6-Fluoro-2-[4-(3-hydroxy-propyl)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline;  
2-[4-(3-Benzoyloxy-propoxy)-phenylamino]-4-phenylamino-quinazoline;  
2-[4-(3-Benzoyloxy-propoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;  
2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(4-methoxy-phenylamino)-quinazoline;  
4-Cyclohexylamino-2-[4-(3-benzoyloxy-propoxy)-phenylamino]-quinazoline;  
2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(3-hydroxy-phenylamino)-quinazoline;  
2-[4-(2-Methoxy-ethoxy)-phenylamino]-4-(3-methoxy-phenylamino)-quinazoline;

4-Cyclohexylamino-2-[4-(3-hydroxy-propoxy)-phenylamino]-quinazoline;  
 4-Cyclohexylamino-2-(4-hydroxy-phenylamino)-quinazoline;  
 4-Cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;  
 4-(4-Chloro-phenylamino)-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;  
 4-(4-Fluoro-phenylamino)-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;  
 4-Cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-quinazoline;  
 4-N-Ethyl-cyclohexylamino-2-[4-(2-methoxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;  
 4-(4-Chloro-phenylamino)-2-[4-(2-methoxyacetyl-aminomethyl)-phenylamino]-8-methoxy-quinazoline;  
 4-Cyclohexylamino-8-methoxy-2-(4-phenylamino)-quinazoline;  
 2,4-Di-(4-chloro-phenylamino)-quinazoline;  
 2-[4-(2-Methoxyacetyl-aminomethyl)-phenylamino]-8-methoxy-4-phenylamino-quinazoline;  
 4-Cyclohexylamino-2-[4-(2-hydroxyethyl)-phenylamino]-quinazoline;  
 2-[4-Aminomethyl)-phenylamino]-4-(4-chloro-phenylamino)-8-methoxy-quinazoline;  
 2-[4-(3-Hydroxy-propoxy)-phenylamino]-4-(3-methyl-phenylamino)-quinazoline;  
 4-Cyclohexylamino-2-[3,4-(methylene-dioxo)-phenylamino]-8-methoxy-quinazoline;  
 2-[3,4-(Methylene-dioxo)-phenylamino]-8-methoxy-4-phenylamino-quinazoline;  
 4-(4-Fluoro-phenylamino)-2-[3,4-(methylene-dioxo)-phenylamino]-8-methoxy-quinazoline;  
 4-(3-Hydroxy-phenylamino)-2-[4-(piperidin-1-yl)-phenylamino]-quinazoline;  
 4-(3-Methyl-phenylamino)-2-[4-(3-benzyloxy-propoxy)-phenylamino]-quinazoline;  
 2-[4-(2-Acetoxy-ethyl)-phenylamino]-4-phenylamino-quinazoline;  
 4-[6-1(H)-Indazol-amino]-2-(4-methoxy-phenylamino)-quinazoline;  
 4-Cyclohexylamino-2-[4-(2-acetoxy-ethyl)-phenylamino]-quinazoline;  
 4-Cyclohexylamino-2-[4-(3-pivaloyloxy-propoxy)-phenylamino]-quinazoline;  
 (S)-2-(4-Methoxy-phenylamino)-4-(1-phenyl-ethylamino)-quinazoline; 4-(4-Chloro-phenylamino)-2-[(2-hydroxy-ethoxy)-phenylamino]-8-methoxy-quinazoline;  
 8-Acetoxy-4-(4-chloro-phenylamino)-2-[(2-methoxy-ethoxy)-phenylamino]-quinazoline;  
 4-Cyclohexylamino-2-(4-chloro-3-methoxy-phenylamino)-8-methoxy-quinazoline; and  
 4-(4-Chloro-3-methoxy-phenylamino)-2-(4-methoxy-phenylamino)-quinazoline; or, in each case, a salt thereof.

11. A pharmaceutical composition for the treatment and prophylaxis of diseases or disorders associated with NPY Y5 receptor subtype comprising a therapeutically effective

amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1.

and a carrier.

12. A pharmaceutical composition according to claim 11 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dyslipidimia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbance, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.

13. A method for the treatment and prophylaxis of diseases or disorders associated with NPY Y5 receptor subtype comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1.

# INTERNATIONAL SEARCH REPORT

Internat. Application No  
PCT/EP 96/05066

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D239/95 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 064 833 A (IFE ET. AL.) 12 November 1991 see claims; examples ---	9
X	EP 0 326 329 A (ELI LILLY & CO.) 2 August 1989 see examples 1,7,24-28,74 ---	9
X	WO 92 14716 A (PFIZER INC.) 3 September 1992 see claims; examples ---	9
X	WO 95 25726 A (RECORDATI S.A. CHEMICAL AND PHARMACEUTICAL CO.) 28 September 1995 see claims; example 28 ---	9
X	WO 92 07844 A (PFIZER INC.) 14 May 1992 see claims; examples 1-71 ---	9
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

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- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

5 May 1997

Date of mailing of the international search report

23.05.97

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Helps, I



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/05066

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 225 866 A (GEROT PHARMAZEUTIKA GMBH) 16 June 1987 see example 2 ---	9
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X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 2, February 1981, WASHINGTON DC, US, pages 127-40, XP000653661 E. F. ELSLAGER ET. AL.: "Synthesis and Antimalarial Effects of N2-Aryl-N4-[(dialkylamino)alkyl]- and N4-Aryl-N2-[(dialkylamino)alkyl]- 2,4-quinazolinediamines." see tables II, III, IV ---	9
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A	EP 0 614 911 A (ELF SANOFI) 14 September 1994 see whole document ---	1-13
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/05066

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 13  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.: 1-13  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
In view of the very broad scope of the claims which include vague defini-  
tions such as "heterocyclic aryl" and "substituted amino", the search has  
been limited to the scope covered by the examples on economic grounds. Some  
of the compounds in claim 10 are not included in the scope of claim 9.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/05066

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Information on patent family members

International Application No

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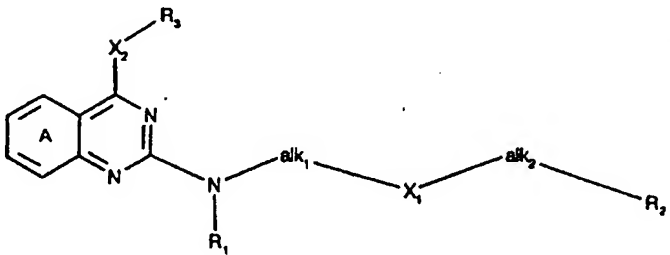
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>C07D 239/95, A61K 31/505</b></p>	<p><b>A2</b></p>	<p>(11) International Publication Number: <b>WO 97/20823</b> (43) International Publication Date: 12 June 1997 (12.06.97)</p>
<p>(21) International Application Number: PCT/EP96/05067 (22) International Filing Date: 18 November 1996 (18.11.96) (30) Priority Data: 08/566,378 1 December 1995 (01.12.95) US (60) Parent Application or Grant (63) Related by Continuation US 08/566,378 (CIP) Filed on 1 December 1995 (01.12.95) (71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basle (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): RÜEGER, Heinrich [CH/CH]; Alemannenweg 6, CH-4112 Flüh (CH). SCHMIDLIN, Tibur [CH/CH]; Friedensgasse 36, CH-4056 Basle (CH). RIGOLLIER, Pascal [FR/FR]; 2, rue Sainte-Catherine, F-68100 Mulhouse (FR). YAMAGUCHI, Yasuchika [JP/CH]; Tellstrasse 44/2, CH-4053 Basle (CH). TINTELNOT-BLOMLEY, Marina [DE/DE]; Röttlerstrasse 1, D-79689 Maulburg (DE). SCHILLING, Walter [CH/CH]; Im Muspenacker, CH-4204 Himmelried (CH). CRISCIONE,</p>		<p>Leoluca [IT/CH]; Kirchstrasse 15, CH-4313 Möhlin (CH). MAH, Robert [CA/CH]; Baslerstrasse 258, CH-4123 Allschwil (CH). (74) Common Representative: NOVARTIS AG; Patent and Trade-mark Dept., Klybeckstrasse 141, CH-4002 Basle (CH). (81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: RECEPTOR ANTAGONISTS</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>The invention relates to a compound of formula (I) in which the variables are as defined and/or a salt or a tautomer thereof; and relates to a method of treatment of disorders or diseases associated with NPY receptor subtype Y5, to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and to the manufacture of the compounds of formula (I) or a salt thereof.</p>		

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## RECEPTOR ANTAGONISTS

### Background of the Invention

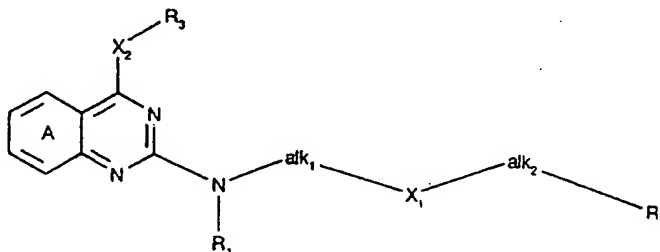
Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family of peptides and is one of the most abundant and widely distributed peptides at the central and peripheral nervous system. NPY acts as a neurotransmitter playing an important role in the regulation of various diseases. Intensive evaluations lead to the finding that multiple NPY receptors are existing being responsible for different physiological and pharmacological activities. Recently, a new NPY receptor subtype has been characterized and cloned, designated as Y5 receptor. It has been demonstrated that the pharmacological function associated with Y5 relates, for example, to obesity and eating disorders. Accordingly, the provision of compounds which act as antagonists of this receptor subtype represents a promisable approach in the regulation of diseases or disorders, such as obesity and eating/food intake disorders.

### Summary of the Invention

The invention relates to new compounds having Y5 antagonistic properties, to pharmaceutical compositions and to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5.

### Detailed Description of the Invention

The invention relates to a compound of formula (I)



in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent, a single bond or lower alkylene;

- 2 -

$R_1$  represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

$R_2$  represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, by carbamoyl, or by N-substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy,  $C_3$ - $C_8$ -cycloalkoxy,  $C_3$ - $C_8$ -cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from  $-CH(OH)-R$ ,  $-CO-R$ ,  $-NR_1-CO-O-R$ ,  $-NR_1-CO-R$ ,  $-NR_1-CO-NR_1-R$ ,  $-NR_1-SO_2-R$ ,  $-NR_1-SO_2-NR_1-R$ ,  $-SO_2-R$ ,  $-SO_2-NR_1-R$ , or  $-SO_2-NR_1-CO-R$ , [R being as defined below and  $R_1$  being as defined above, or the group  $-N(R)(R_1)$  represents amino which is di-substituted by lower alkylene (which may be interrupted by O,  $S(O)_n$  or  $NR_0$ ) or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula  $-X_3(X_4)(X_5)$  wherein, (a) if  $X_3$  is  $-CH-$ ,  $X_4$  together with  $X_5$  represent a structural element of formula  $-X_6-(CO)_p-(CH_2)_o-$ ,  $-(CH_2)_q-X_6-(CO)_p-(CH_2)_r-$ , or  $-(CH_2)_s-X_6-CO-(CH_2)_t-$ ; or, (b) if  $X_3$  is  $-N-$ ,  $X_4$  together with  $X_5$  represent a structural element of formula  $-CO-(CH_2)_u-$ ; [ $X_6$  being  $-CH_2-$ ,  $-N(R_1)-$  or  $-O-$ ; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0,  $X_4$  is different from  $-CH_2-$ ];

$X_1$  represents  $C_3$ - $C_8$ -cycloalkylene,  $C_3$ - $C_8$ -cycloalkenylene,  $C_3$ - $C_8$ -cycloalkylidene,  $C_3$ - $C_8$ -cycloalkenyliidene, oxo- $C_3$ - $C_8$ -cycloalkylene, oxo- $C_3$ - $C_8$ -cycloalkenylene, oxo- $C_3$ - $C_8$ -cycloalkylidene, or oxo- $C_3$ - $C_8$ -cycloalkenyliidene;

$X_2$  represents -O-,  $-S(O)_n-$  or a group of the formula  $-N(R_4)-$ ;

$R_3$  and  $R_4$ , independently of one another, represent

- (i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and  $-S(O)_n-R$ ;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ ,  $NR_0$ ] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

- (i) halogen, lower alkyl, lower alkenyl, lower alkynyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3-C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iv) amino, substituted amino;
- (v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO<sub>2</sub>-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy; or a salt or a tautomer thereof; and relates to a method of treatment of associated with NPY receptor subtype Y5, to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and to the manufacture of the compounds of formula (I) or a salt thereof.

Compounds of formula (I) in which X<sub>2</sub>-R<sub>3</sub> represent -OH or -SH, are present in form of proton tautomers i.e. in a kind of enol-keto tautomeric forms. Corresponding tautomers also are an embodiment of the present invention.

The compounds (I) can be present as salts, in particular pharmaceutically acceptable salts. If the compounds (I) have, for example, at least one basic centre, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as C<sub>1</sub>-C<sub>4</sub>-alkanecarboxylic acids which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic

or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or such as benzoic acid, or with organic sulfonic acids, such as C<sub>1</sub>-C<sub>4</sub>-alkane- or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluenesulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic centre. The compounds (I) having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed, if a compound of formula comprises e.g. both a carboxy and an amino group. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds (I) or their pharmaceutically acceptable salts, are also included.

(Carbocyclic or heterocyclic) aryl in (carbocyclic or heterocyclic) aryl or aryloxy, respectively, represents, for example, phenyl, biphenyl, naphthyl or an appropriate 5- or 6-membered and monocyclic radical or an appropriate bicyclic heteroaryl radical which, in each case, have up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom. Appropriate 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered radicals are in particular pyridyl. Appropriate bicyclic heterocyclic aryls are, for example, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinoliny, isoquinoliny, or quinazolinyl. Appropriate aromatic radicals, including ring A, are radicals which may be monosubstituted or polysubstituted, for example di- or trisubstituted, for example by identical or different radicals, for example selected from the group as given above. Preferred substituents of corresponding aryl radicals (including of ring A) are, for example, halogen, lower alkyl, halo-

lower alkyl, lower alkoxy, oxy-lower alkylene-oxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

(Carbocyclic or heterocyclic) aroyl is in particular benzoyl, naphthoyl, furoyl, thenoyl, or pyridoyl.

(Carbocyclic or heterocyclic) aryl-lower alkanoyl in (carbocyclic or heterocyclic) aryl-lower alkanoyloxy or (carbocyclic or heterocyclic) aryl-lower alkanoyl is in particular phenyl-lower alkanoyl, naphthyl-lower alkanoyl, or pyridyl-lower alkanoyl,

(Carbocyclic or heterocyclic) aryl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-lower alkyl.

(Carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl is in particular phenyl-, naphthyl- or pyridyl-lower alkoxy.

(Carbocyclic or heterocyclic) arylene represents, in particular, phenylene, naphthylene, thiophenylene, furylene, pyridylene which may be substituted, for example, as indicated for benzo ring A or preferably unsubstituted.

Lower alkyl which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, phenoxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl, amino-lower alkyl, or N- or N,N- substituted amino-lower alkyl.

An amino group which is mono-substituted by lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl is in particular lower alkyl-amino, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-amino, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-loweralkyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl-amino.

An amino group which is, independently of one another, di-substituted by lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or

heterocyclic) aryl-lower alkyl is in particular di-lower alkylamino, di- $C_3$ - $C_8$ -cycloalkyl-amino, di-( $C_3$ - $C_8$ -cycloalkyl-lower alkyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino, lower alkyl- $C_3$ - $C_8$ -cycloalkyl-amino, lower alkyl-( $C_3$ - $C_8$ -cycloalkyl-lower alkyl)-amino, lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-amino, lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino.

Lower alkyl which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, NR<sub>0</sub>, the integer n being 0, 1 or 2 and R<sub>0</sub> being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO<sub>3</sub>H, -SO<sub>2</sub>-R and R being lower alkyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl] is in particular carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, lower alkoxy-lower alkoxy-carbonyl-lower alkyl, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, or corresponding N- or N,N-substituted carbamoyl-lower alkyl.

Lower alkoxy which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy, amino-lower alkoxy, or corresponding N- or N,N- substituted amino-lower alkoxy.

Lower alkoxy which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, NR<sub>0</sub>,

the integer  $n$  being 0, 1 or 2 and  $R_0$  being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl,  $-SO_3H$ ,  $-SO_2-R$  and  $R$  being lower alkyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl] is in particular carboxy-lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, lower alkoxy-lower alkoxy-carbonyl-lower alkoxy, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxy-carbonyl-lower alkoxy, carbamoyl-lower alkoxy,  $N$ - or  $N,N$ -substituted carbamoyl-lower alkoxy.

Substituted lower alkyl or lower alkoxy, respectively, is mono- or poly-substituted, e.g. di- or tri-substituted.

The group of formula  $-N(R_3)(R_4)$  [ $X_2 = -N(R_4)-$ ] in which  $R_3$  and  $R_4$  together represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring represents, for example, lower alkylene-phenylene-lower alkylene-amino, such as 3,4-dihydro-1*H*-isoquinolin-2-yl.

The general definitions used above and below, unless defined differently, have the following meanings:

The expression "lower" means that corresponding groups and compounds, in each case, in particular comprise not more than 7, preferably not more than 4, carbon atoms.

Halogen is in particular halogen of atomic number not more than 35, such as fluorine, chlorine or bromine, and also includes iodine.

Lower alkyl is in particular  $C_1-C_7$ -alkyl, for example methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, and also includes corresponding pentyl, hexyl and heptyl radicals.  $C_1-C_4$ -alkyl is preferred.

Lower alkenyl is in particular  $C_3-C_7$ -alkenyl and is, for example, 2-propenyl or 1-, 2- or 3-butenyl.  $C_3-C_5$ -alkenyl is preferred.



Lower alkynyl is in particular C<sub>3</sub>-C<sub>7</sub>-alkynyl and is preferably propargyl.

Lower alkoxy is in particular C<sub>1</sub>-C<sub>7</sub>-alkoxy and is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy and also includes corresponding pentyloxy, hexyloxy and heptyloxy radicals. C<sub>1</sub>-C<sub>4</sub>-alkoxy is preferred.

Lower alkenyloxy is in particular C<sub>3</sub>-C<sub>7</sub>-alkenyloxy, preferably allyloxycarbonyl, while lower alkynyloxy is in particular C<sub>3</sub>-C<sub>5</sub>-alkynyloxy, such as propargyloxy.

Oxy-lower alkylene-oxy is in particular oxy-C<sub>1</sub>-C<sub>4</sub>-alkylene-oxy, preferably oxy-methylene-oxy or oxy-ethylene-oxy.

Lower alkanoyl is in particular C<sub>2</sub>-C<sub>7</sub>-alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C<sub>2</sub>-C<sub>5</sub>-alkanoyl is preferred.

Lower alkanoyl-oxy is in particular C<sub>2</sub>-C<sub>7</sub>-alkanoyl-oxy, such as acetyl-oxy, propionyl-oxy, butyryl-oxy, isobutyryl-oxy or pivaloyl-oxy. C<sub>2</sub>-C<sub>5</sub>-alkanoyl-oxy is preferred.

Naphthoyl is 1- or 2-naphthoyl, furoyl 2- or 3-furoyl, thenoyl 2- or 3-thenyl, and pyridoyl 2-, 3-, or 4-pyridoyl.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-lower alkyl is in particular C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, in particular C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-C<sub>1</sub>-C<sub>2</sub>-alkyl. Preferred is cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkoxy is, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy. Cyclopentyloxy and cyclohexyloxy are preferred.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-lower alkoxy is in particular C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, in particular C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-C<sub>1</sub>-C<sub>2</sub>-alkoxy. Preferred is cyclopropylmethoxy, cyclopentylmethoxy or cyclohexylmethoxy.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkylene is, for example, C<sub>3</sub>-C<sub>6</sub>-cycloalkylene, such as 1,3-cyclopentylene, 1,3- or 1,4-cyclohexylene, or 1,4-.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkenylene is, for example, C<sub>3</sub>-C<sub>6</sub>-cycloalkenylene, such as 1,3-cyclopent-2-enylene, 1,3- or 1,4-cyclohex-2-enylene.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkylidene is, for example, C<sub>3</sub>-C<sub>6</sub>-cycloalkylidene, such as cyclopentylidene, cyclopentylidene or cyclohexylidene.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkenylidene is, for example, C<sub>3</sub>-C<sub>6</sub>-cycloalkenylidene, such as 1,1-cyclopent-2-enylidene, 1,1-cyclohex-2-enylidene or 1,1-cyclohex-3-enylidene.

Oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylene is, for example, oxo-C<sub>3</sub>-C<sub>6</sub>-cycloalkylene, such as 2-oxo-1,3-cyclopentylene, 2-oxo-1,3- or 2-oxo-1,4-cyclohexylene or 3-oxo-1,3- or 3-oxo-1,4-cyclohexylene.

Oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene is, for example, oxo-C<sub>3</sub>-C<sub>6</sub>-cycloalkenylene, such as 2-oxo-1,3-cyclopent-5-enylene, 2-oxo-1,3- or 2-oxo-1,4-cyclohex-5-enylene, or 3-oxo-1,4-cyclohex-5-enylene.

Oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene is, for example, oxo-C<sub>3</sub>-C<sub>6</sub>-cycloalkylidene, such as 2-oxo-1,1-cyclopent-5-enylidene, 2-oxo-1,3- or 2-oxo-1,4-cyclohexenylidene or 3-oxo-1,3- or 3-oxo-1,4-cyclohex-5-enylidene.

Oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkenylidene is, for example, oxo-C<sub>3</sub>-C<sub>6</sub>-cycloalkenylidene, such as 2-oxo-1,1-cyclopent-3-enylidene or 2- or 3-oxo-1,1-cyclohex-5-enylidene.

Lower alkylene is in particular C<sub>1</sub>-C<sub>7</sub>-alkylene, in particular C<sub>1</sub>-C<sub>5</sub>-alkylene, and is straight-chain or branched and is in particular methylene, ethylene, propylene and butylene and also 1,2-propylene, 2-methyl-1,3-propylene, 3-methyl-1,5-pentylene

and 2,2-dimethyl-1,3-propylene. C<sub>3</sub>-C<sub>5</sub>-alkylene is preferred. In case of alk<sub>1</sub> or alk<sub>2</sub>, respectively, lower alkylene preferably is -(CH<sub>2</sub>)<sub>p</sub>- the integer p being 1-3. Lower alkylene in an substituted amino group preferably is 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, 2-methyl-1,3-propylene, or 2-methyl-butylene, or 3-methyl-1,5-pentylene.

Amino which is di-substituted by lower alkylene is in particular C<sub>3</sub>-C<sub>7</sub>-alkyleneamino, preferably 1-azidino, 1-pyrrolidino or 1-piperidino.

Amino which is di-substituted by lower alkylene which is interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub> is in particular morpholino, thiomorpholino or the mono- or di-oxide thereof, or 4-R<sub>0</sub>-piperazino.

Lower alkanesulfonyl is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>5</sub>-alkoxycarbonyl, preferably ethoxyethoxycarbonyl, methoxyethoxycarbonyl and isopropoxyethoxycarbonyl.

Lower alkoxycarbonyl is in particular C<sub>2</sub>-C<sub>8</sub>-alkoxycarbonyl and is, for example, methoxy-, ethoxy-, propyloxy- or pivaloyloxy-carbonyl. C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl is preferred.

Lower alkoxy-lower alkoxy-carbonyl is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl and is, for example, methoxy- or ethoxy-ethoxy-alkoxycarbonyl.

Hydroxy-lower alkyl is in particular hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl. Furthermore, hydroxy-lower alkyl may exhibit two hydroxy groups, such as 3-hydroxy-1-hydroxymethyl-propyl.

Hydroxy-lower alkoxy is in particular hydroxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

Lower alkoxy-lower alkoxy is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy and is, for example, (m)ethoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2-n-propyloxyethoxy or ethoxymethoxy.

Amino which is di-substituted by lower alkylene and is condensed at two adjacent carbon atoms with a benzene ring is in particular C<sub>2</sub>-C<sub>6</sub>-cycloalkylenemino which is condensed at two adjacent carbon atoms with a benzene ring. Preferred is indolin-1-yl or 1,2,3,4-tetrahydro-quinolin-1-yl.

Halo-lower alkyl is in particular halo-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as trifluoromethyl, 1,1,2-trifluoro-2-chloroethyl or chloromethyl.

Halo-lower alkoxy is in particular halo-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as trifluoromethoxy, 1,1,2-trifluoro-2-chloroethoxy or chloromethoxy.

Phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl is in particular phenyloxy-, naphthyloxy- or pyridyloxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as phenoxy-methyl, 2-phenoxy-ethyl, 1- or 2-naphthyloxy-methyl, or 2-, 3-, or 4-pyridyloxy-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as phenyl-methyl, 2-phenyl-ethyl, 1- or 2-naphthyl-methyl, or 2-, 3-, or 4-pyridyl-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy is in particular phenyl-, naphthyl- or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as phenyl-methoxy, 2-phenyl-ethoxy, 1- or 2-naphthyl-methoxy, or 2-, 3-, or 4-pyridyl-methoxy.

Naphthyl is in particular 1- or 2-naphthyl; furyl 2- or 3-furyl; thienyl 2- or 3-thienyl; pyridyl 2-, 3- or 4-pyridyl, indolyl e.g. 1-, 2-, 3- or 5-indolyl, indazolyl e.g. 6-1(H)-indazolyl, benzofuryl e.g. 2-, 3- or 5-benzofuranyl, benzothienyl e.g. 2-, 3-, or 5-benzothienyl, benzimidazolyl e.g. 1-, 2- or 5-benzimidazolyl, quinolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinolinyl, isoquinolinyl e.g. 1-, 3-, 4-, or 6-isoquinolyl, or quinazolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl.

Amino-lower alkyl is in particular amino-C<sub>1</sub>-C<sub>7</sub>-alkyl, preferably amino-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as aminomethyl, 2-aminoethyl or 3-aminopropyl.

Lower alkylamino is in particular C<sub>1</sub>-C<sub>7</sub>-alkylamino and is, for example, methyl-, ethyl-, n-propyl- and isopropyl-amino. C<sub>1</sub>-C<sub>4</sub>-alkylamino is preferred.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-amino is in particular C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-amino and is, for example, cyclopropyl-, cyclopentyl- and cyclohexyl-amino.

C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-lower alkylamino is in particular C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>7</sub>-alkylamino and is, for example, cyclopropylmethyl-amino or cyclohexylmethyl-amino. C<sub>3</sub>-C<sub>8</sub>-Cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkylamino is preferred.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl-amino is in particular phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkyl-amino, preferably benzyl-amino, 2-phenethyl-amino, 1- or 2-naphthylmethyl-amino, or 2-, 3-, or 4-pyridylmethyl-amino.

Di-lower alkylamino is in particular di-C<sub>1</sub>-C<sub>4</sub>-alkylamino, such as dimethyl-, diethyl-, di-n-propyl-, methylpropyl-, methylethyl-, methylbutyl-amino and dibutylamino.

Di-C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-amino is in particular di-C<sub>3</sub>-C<sub>6</sub>-cycloalkylamino, preferably cyclopropylamino, cyclopentylamino or cyclohexylamino.

Di-(C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl)-amino is in particular di-(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl)-amino, preferably cyclopropylmethyl-amino, cyclopentylmethyl-amino or cyclohexylmethyl-amino.

Di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkyl)-amino, preferably di-benzyl-amino, di-(2-phenethyl)-amino, di-(1- or 2-naphthylmethyl)-amino, or di-(2-, 3-, or 4-pyridylmethyl)-amino.

Lower alkyl-C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-amino is in particular C<sub>1</sub>-C<sub>4</sub>-alkyl-C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-amino, preferably methyl-cyclopropyl-amino, methyl-cyclopentyl-amino or methyl-cyclohexyl-amino.

Lower alkyl-(C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl)-amino is in particular C<sub>1</sub>-C<sub>4</sub>-alkyl-(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl-C<sub>1</sub>-C<sub>4</sub>-alkyl)amino, preferably methyl-cyclopropylmethyl-amino, methyl-cyclopentylmethyl-amino or methyl-cyclohexylmethyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino is in particular C<sub>1</sub>-C<sub>4</sub>-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino, such as (m)ethyl-phenyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular C<sub>1</sub>-C<sub>4</sub>-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C<sub>1</sub>-C<sub>4</sub>-alkyl)-amino, such as (m)ethyl-benzyl-amino or (m)ethyl-(2-phenethyl)-amino.

Carboxy-lower alkyl is in particular carboxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as carboxy-methyl, 2-carboxy-ethyl, or 3-carboxy-propyl.

Lower alkoxy-carbonyl-lower alkyl is in particular C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as (m)ethoxycarbonyl-methyl, 2-(m)ethoxycarbonyl-ethyl or 2-pivaloyl-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkyl is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as 2-methoxy-ethoxycarbonyl-methyl or 2-(2-ethoxy-ethoxycarbonyl)-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxy-carbonyl-lower alkyl is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as benzyloxycarbonyl-methyl or 2-(2-phenethyloxy-carbonyl)-ethyl.

Carbamoyl-lower alkyl is in particular carbamoyl-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as carbamoyl-methyl, 2-carbamoyl-ethyl or 3-carbamoyl-propyl.

Amino-lower alkoxy is in particular amino-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as aminomethoxy, 2-aminoethoxy, or 3-amino-propoxy.

Carboxy-lower alkoxy is in particular carboxy-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as carboxy-methoxy, 2-carboxy-ethoxy, or 3-carboxy-propyloxy.

Lower alkoxy-carbonyl-lower alkoxy is in particular C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as (m)ethoxycarbonyl-methoxy, 2-methoxycarbonyl-ethyl, or 2-(2-ethoxycarbonyl)-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkoxy is in particular C<sub>1</sub>-C<sub>4</sub>-alkoxy-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as (m)ethoxymethoxycarbonyl-methoxy, 2-ethoxymethoxycarbonyl-ethyl, or 2-[(2-ethoxy-ethoxycarbonyl)]-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxy-carbonyl-lower alkoxy is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C<sub>2</sub>-C<sub>5</sub>-alkoxycarbonyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as benzyloxycarbonyl-methoxy, phenethyloxycarbonyl-methoxy, 2-(benzyloxycarbonyl)-ethoxy, or 2-(2-phenethyloxycarbonyl)-ethoxy.

Carbamoyl-lower alkoxy is in particular carbamoyl-C<sub>1</sub>-C<sub>4</sub>-alkoxy, such as carbamoyl-methoxy, 2-carbamoyl-ethoxy, or 3-carbamoyl-propyloxy.

Obesity, for example, is a wide-spread phenomena which e.g. causes a variety of pathological symptoms or influences the overall state of health. Also associated therewith are considerable socio-economic investments and a heavy financial burden for managed health care organisations. The problem to be solved is to present an approach to systemically treat obesity or related diseases or disorders. Surprisingly, it has been manifested that the modulation of the NPY receptor subtype Y5 leads to a control of the eating behavior.

Extensive pharmacological investigations have shown that the compounds (I) and their pharmaceutically acceptable salts, for example, are useful as antagonists of the neuropeptide Y5 receptor subtype.

Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family with wide-spread distribution throughout the mammalian nervous system. NPY and its relatives (peptide YY or PYY, and pancreatic polypeptide or PP) elicit a broad range of physiological effects through activation of at least five G protein-coupled receptor subtypes known as Y1, Y2, Y3, Y4 (or PP), and the "atypical Y1". The role of NPY as the most powerful stimulant of feeding behavior yet described is thought to occur primarily through activation of the hypothalamic "atypical Y1" receptor. This receptor is unique in that its classification is based solely on feeding behavior data, rather than radioligand binding data, unlike the Y1, Y2, Y3, and Y4 (or PP) receptors, each of which are described previously in both radioligand binding and functional assays. <sup>125</sup>I-PYY-

based expression cloning technique may be used to isolate a rat hypothalamic cDNA encoding an "atypical Y1" receptor referred to herein as the Y5 subtype. Y5 homolog may be isolated and characterized of from human hippocampus. Protein sequence analysis reveals that the Y5 receptor belongs to the G protein- coupled receptor superfamily. Both the human and rat homolog display  $\leq 42\%$  identity in transmembrane domains with the previously cloned "Y-type" receptors. Rat brain localization studies using in situ hybridization techniques verify the existence of Y5 receptor mRNA in rat hypothalamus. Pharmacological evaluation reveals the following similarities between the Y5 and the "atypical Y1" receptor. 1) Peptides bind to the Y5 receptor with a rank order of potency identical to that described for the feeding response: NPY  $\geq$  NPY<sub>2-36</sub> = PYY = [Leu<sup>31</sup>, Pro<sup>34</sup>]NPY  $\gg$  NPY<sub>13-36</sub>. 2) The Y5 receptor is negatively coupled to cAMP accumulation, as has been proposed for the "atypical Y1" receptor. 3) Peptides activate the Y5 receptor with a rank order of potency identical to that described for the feeding response. 4) The reported feeding "modulator" [D-Trp<sup>32</sup>]NPY binds selectively to the Y5 receptor and subsequently activated the receptor. 5) Both the Y5 and the "atypical Y1" receptors are sensitive to deletions or modifications in the midregion of NPY and related peptide ligands.

The peptide neurotransmitter neuropeptide Y (NPY) is a 36 amino acid member of the pancreatic polypeptide family with widespread distribution throughout the mammalian nervous system. NPY is considered to be the most powerful stimulant of feeding behavior yet described (Clark, J.T., Kalra, P.S., Crowley, W.R., and Kalra, S.P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. Endocrinology 115: 427-429, 1984; Levine, A.S., and Morley, J.E. (1984). Neuropeptide Y: A potent inducer of consummatory behavior in rats. Peptides 5: 1025-1029; Stanley, B.G., and Leibowitz, S.F.; (1984) Neuropeptide Y: Stimulation of feeding and drinking by injection into the paraventricular nucleus. Life Sci. 35: 2635-2642). Direct injection into the hypothalamus of satiated rats, for example, can increase food intake up to 10-fold over a 4-hour period (Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y<sub>1</sub> receptor mediating this peptide's effect. Peptides 13: 581-587). The role of NPY in normal and abnormal eating behavior, and the ability to interfere with NPY-dependent pathways as a means to appetite and weight control, are areas of great interest in pharmacological and pharmaceutical research (Sahu and Kalra, 1993; Dryden, S., Frankish, H., Wang, Q., and Williams, G. (1994). Neuropeptide Y and energy balance: one way ahead for the treatment of obesity? Eur. J. Clin. Invest. 24: 293-308). Any credible means of studying or controlling NPY-dependent feeding behavior, however, must



necessarily be highly specific as NPY can act through at least 5 pharmacologically defined receptor subtypes to elicit a wide variety of physiological functions (Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167). It is therefore vital that knowledge of the molecular biology and structural diversity of the individual receptor subtypes be understood as part of a rational drug design approach to develop subtype selective compounds. A brief review of NPY receptor pharmacology is summarized below and also in Table 1.

TABLE 1: Pharmacologically defined receptors for NPY and related pancreatic polypeptides.

Rank orders of affinity for key peptides (NPY, PYY, PP, [Leu<sup>31</sup>,Pro<sup>34</sup>]NPY, NPY<sub>2-36</sub>, and NPY<sub>13-36</sub>) are based on previously reported binding and functional data (Schwartz, T.W., J. Fuhlendorff, L.L.Kjems, M.S. Kristensen, M. Vervelde, M. O'Hare, J.L. Krstenansky, and B. Bjornholm. (1990). Signal epitopes in the three-dimensional structure of neuropeptide Y. Ann. N.Y. Acad. Sci. 611: 35-47; Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082; Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167; Wahlestedt, C., and D.J. Reis. (1993). Neuropeptide Y-Related Peptides and Their Receptors--Are the Receptors Potential Therapeutic Targets? Ann. Rev. Pharmacol. Tox. 32: 309-352). Missing peptides in the series reflect a lack of published information.

TABLE 1

Receptor	Affinity (pK <sub>i</sub> or pEC <sub>50</sub> )					
	11 to 10	10 to 9	9 to 8	8 to 7	7 to 6	< 6
Y1	NPY PYY [Leu <sup>31</sup> ,Pro <sup>34</sup> ] NPY		NPY <sub>2-36</sub>	NPY <sub>13-36</sub>	PP	
Y2		PYY NPY NPY <sub>2-36</sub>	NPY <sub>13-36</sub>			[Leu <sup>31</sup> , Pro <sup>34</sup> ] NPY PP
Y3		NPY	[Pro <sup>34</sup> ] NPY	NPY <sub>13-36</sub> PP		PYY
Y4	PP	PYY [Leu <sup>31</sup> ,Pro <sup>34</sup> ] NPY	NPY NPY <sub>2-36</sub>	NPY <sub>13-36</sub>		
Y5		PYY NPY NPY <sub>2-36</sub> [Leu <sup>31</sup> ,Pro <sup>34</sup> ] NPY		NPY <sub>13-36</sub>		

### NPY Receptor Pharmacology

NPY receptor pharmacology has historically been based on structure/activity relationships within the pancreatic polypeptide family. The entire family includes the namesake pancreatic polypeptide (PP), synthesized primarily by endocrine cells in the pancreas; peptide YY (PYY), synthesized primarily by endocrine cells in the gut; and NPY, synthesized primarily in neurons (Michel, M.C. (1991). Receptors for neuropeptide Y: multiple subtypes and multiple second messengers. Trends Pharmacol.: 12: 389-394; Dumont et al., 1992; Wahlestedt and Reis, 1993). All pancreatic polypeptide family members share a compact structure involving a "PP-fold" and a conserved C-terminal hexapeptide ending in Tyr<sup>36</sup> (or Y<sup>36</sup> in the single letter code). The striking conservation of Y<sup>36</sup> has prompted the reference to the pancreatic polypeptides' receptors as "Y-type" receptors (Wahlestedt, C., L. Edvinsson, E. Ekblad, and R. Hakanson. Effects of neuropeptide Y at sympathetic neuroeffector junctions: Existence of Y<sub>1</sub> and Y<sub>2</sub> receptors. In: Neuronal messengers in vascular function, Fernstrom Symp. No 10., pp. 231-242. Eds A. Nobin and C.H. Owman. Elsevier: Amsterdam (1987)), all of which are proposed to function as seven transmembrane-spanning G protein-coupled receptors (Dumont et al., 1992).

The Y1 receptor recognizes NPY = PYY >> PP (Grundemar et al., 1992). The receptor requires both the N- and the C-terminal regions of the peptides for optimal recognition. Exchange of Gln<sup>34</sup> in NPY or PYY with the analogous residue from PP (Pro<sup>34</sup>), however, is well-tolerated. The Y1 receptor has been cloned from a variety of species including human, rat and mouse (Larhammar, D., A.G. Blomqvist, F. Yee, E. Jazin, H. Yoo, and C. Wahlestedt. (1992). Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y1 type. J. Biol. Chem. 267: 10935-10938; Herzog, H., Y.J. Hort, H.J. Ball, G. Hayes, J. Shine, and L. Selbie. (1992). Cloned human neuropeptide Y receptor couples to two different second messenger systems. Proc. Natl. Acad. Sci. USA 89, 5794-5798; Eva, C., Oberto, A., Sprengel, R. and E. Genazzani. (1992). The murine NPY-1 receptor gene: structure and delineation of tissue specific expression. FEBS Lett. 314: 285-288; Eva, C., Keinänen, K., Monyer, H., Seeburg, P., and Sprengel, R. (1990). Molecular cloning of a novel G protein-coupled receptor that may belong to the neuropeptide receptor family. FEBS Lett. 271, 80-84). The Y2 receptor recognizes PYY ~ NPY >> PP and is relatively tolerant of N-terminal deletion (Grundemar, L. and R. Hakanson (1994). Neuropeptide Y effector systems:

perspectives for drug development. Trends. Pharmacol. 15:153-159). The receptor has a strict requirement for structure in the C-terminus (Arg<sup>33</sup>-Gln<sup>34</sup>-Arg<sup>35</sup>-Tyr<sup>36</sup>-NH<sub>2</sub>); exchange of Gln<sup>34</sup> with Pro<sup>34</sup>, as in PP, is not well tolerated. The Y2 receptor has recently been cloned. The Y3 receptor is characterized by a strong preference for NPY over PYY and PP (Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082). [Pro<sup>34</sup>]NPY is reasonably well tolerated even though PP, which also contains Pro<sup>34</sup>, does not bind well to the Y3 receptor. This receptor (Y3) has not yet been cloned. The Y4 receptor binds PP > PYY > NPY. Like the Y1, the Y4 requires both the N- and the C-terminal regions of the peptides for optimal recognition. The "atypical Y1" or "feeding" receptor is defined exclusively by injection of several pancreatic polypeptide analogs into the paraventricular nucleus of the rat hypothalamus which stimulates feeding behavior with the following rank order: NPY<sub>2-36</sub> ≥ NPY ~ PYY ~ [Leu<sup>31</sup>,Pro<sup>34</sup>]NPY > NPY<sub>13-36</sub> (Kalra, S.P., Dube, M.G., Fournier, A., and Kalra, P.S. (1991). Structure-function analysis of stimulation of food intake by neuropeptide Y: Effects of receptor agonists. Physiology & Behavior 50: 5-9; Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y<sub>1</sub> receptor mediating this peptide's effect. Peptides 13: 581-587). The profile is similar to that of a Y1-like receptor except for the anomalous ability of NPY<sub>2-36</sub> to stimulate food intake with potency equivalent or better than that of NPY. A subsequent report by Balasubramaniam, A., Sheriff, S., Johnson, M.E., Prabhakaran, M., Huang, Y., Fischer, J.E., and Chance, W.T. (1994). [D-Trp<sup>32</sup>]Neuropeptide Y: A competitive antagonist of NPY in rat hypothalamus. J. Med. Chem. 37: 311-815 showed that feeding can be regulated by [D-Trp<sup>32</sup>]NPY. While this peptide is presented as an NPY antagonist, the published data at least in part support a stimulatory effect of [D-Trp<sup>32</sup>]NPY on feeding. [D-Trp<sup>32</sup>]NPY thereby represents another diagnostic tool for receptor identification.

This plasmid (pcEXV-hY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Accession No. 75943.

The plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the rat Y5 receptor as to permit expression thereof has been designated as pcEXV-rY5 (ATCC Accession No. 75944).

This plasmid (pcEXV-rY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Accession No. CRL 75944.

A method for determining whether a ligand can specifically bind to a Y5 receptor comprises contacting a cell transfected with and expressing DNA encoding the Y5 receptor with the ligand under conditions permitting binding of ligands to such receptor, detecting the presence of any such ligand specifically bound to the Y5 receptor, and thereby determining whether the ligand specifically binds to the Y5 receptor.

A method for determining whether a ligand is a Y5 receptor antagonist comprises contacting a cell transfected with and expressing DNA encoding a Y5 receptor with the ligand in the presence of a known Y5 receptor agonist, such as PYY or NPY, under conditions permitting the activation of a functional Y5 receptor response, detecting a decrease in Y5 receptor activity, and thereby determining whether the ligand is a Y5 receptor antagonist.

In an embodiment of the above-described methods, the cell is non-neuronal in origin. In a further embodiment, the non-neuronal cell is a COS-7 cell, 293 human embryonic kidney cell, NIH-3T3 cell or L-M(TK-) cell.

The cell lines are transfected with a vector which is adapted for expression in a mammalian cell which comprises the regulatory elements necessary for expression of the DNA in the mammalian cell operatively linked to the DNA encoding the mammalian Y5 receptor as to permit expression thereof.

For example, such plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the human

Y5 receptor as to permit expression thereof designated pcEXV-hY5 (ATCC Accession No. 75943).

### Experimental Details

## MATERIALS AND METHODS

### cDNA Cloning

Total RNA was prepared by a modification of the guanidine thiocyanate method (Kingston, 1987), from 5 grams of rat hypothalamus (Rockland, Gilbertsville, PA). Poly A<sup>+</sup>RNA was purified with a FastTrack kit (Invitrogen Corp., San Diego, CA). Double stranded (ds) cDNA was synthesized from 7 mg of poly A<sup>+</sup> RNA according to Gubler and Hoffman (Gubler, U abd B.J. Hoffman. (1983). A simple and very efficient method for generating cDNA libraries. Gene. 25, 263-269), except that ligase was omitted in the second strand cDNA synthesis. The resulting DS cDNA was ligated to BstXI/EcoRI adaptors (Invitrogen Corp.), the excess of adaptors was removed by chromatography on Sephacryl 500 HR (Pharmacia®-LKB) and the ds-cDNA size selected on a Gen-Pak Fax HPLC column (Millipore Corp., Milford, MA). High molecular weight fractions were ligated in pEXJ.BS (A cDNA cloning expression vector derived from pcEXV-3; Okayama, H. and P. Berg (1983). A cDNA cloning vector that permits expression of cDNA inserts in mammalian cells. Mol. Cell. Biol. 3: 280-289; Miller, J. and Germain, R.N. (1986). Efficient cell surface expression of class II MHC molecules in the absence of associated invariant chain. J. Exp. Med. 164: 1478-1489) cut by BstXI as described by Aruffo and Seed (Aruffo, A. and Seed, B. (1987). Molecular cloning of a CD28 cDNA by a high efficiency COS cell expression system. PNAS, 84, 8573-8577). The ligated DNA was electroporated in E.Coli MC 1061 F<sup>+</sup> (Gene Pulser, Biorad). A total of  $3.4 \times 10^6$  independent clones with an insert mean size of 2.7 kb could be generated. The library was plated on Petri dishes (Ampicillin selection) in pools of  $6.9$  to  $8.2 \times 10^3$  independent clones. After 18 hours amplification, the bacteria from each pool were scraped, resuspended in 4 ml of LB media and 1.5 ml processed for plasmid purification with a QIAprep-8 plasmid kit (Qiagen Inc, Chatsworth, CA). 1 ml aliquots of each bacterial pool were stored at -85°C in 20% glycerol.

Isolation of a cDNA clone encoding an atypical rat hypothalamic NPY5 receptor

DNA from pools of » 7500 independent clones was transfected into COS-7 cells by a modification of the DEAE-dextran procedure (Warden, D. and H.V. Thorne. (1968). Infectivity of polyoma virus DNA for mouse embryo cells in presence of diethylaminoethyl-dextran. J. Gen. Virol. 3, 371). COS-7 cells were grown in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal calf serum, 100 U/ml of penicillin, 100 mg/ml of streptomycin, 2 mM L-glutamine (DMEM-C) at 37°C in 5% CO<sub>2</sub>. The cells were seeded one day before transfection at a density of 30,000 cells/cm<sup>2</sup> on Lab-Tek chamber slides (1 chamber, Permanox slide from Nunc Inc., Naperville, IL). On the next day, cells were washed twice with PBS, 735 µl of transfection cocktail was added containing 1/10 of the DNA from each pool and DEAE-dextran (500 mg/ml) in Opti-MEM I serum free media (Gibco®BRL Life Technologies Inc. Grand Island, NY). After a 30 min. incubation at 37°C, 3 ml of chloroquine (80 mM in DMEM-C) was added and the cells incubated a further 2.5 hours at 37°C. The media was aspirated from each chamber and 2 ml of 10% DMSO in DMEM-C added. After 2.5 min. incubation at room temperature, the media was aspirated, each chamber washed once with 2 ml PBS, the cells incubated 48 hours in DMEM-C and the binding assay was performed on the slides. After one wash with PBS, positive pools were identified by incubating the cells with 1 nM (3x10<sup>6</sup> cpm per slide) of porcine [<sup>125</sup>I]-PYY (NEN; SA=2200 Ci/mmol) in 20 mM Hepes-NaOH pH 7.4, CaCl<sub>2</sub> 1.26 mM, MgSO<sub>4</sub> 0.81 mM, KH<sub>2</sub>PO<sub>4</sub> 0.44 mM, KCL 5.4, NaCl 10 mM, .1% BSA, 0.1% bacitracin for 1 hour at room temperature. After six washes (three seconds each) in binding buffer without ligand, the monolayers were fixed in 2.5% glutaraldehyde in PBS for five minutes, washed twice for two minutes in PBS, dehydrated in ethanol baths for two minutes each (70, 80, 95, 100%) and air dried. The slides were then dipped in 100% photoemulsion (Kodak® type NTB2) at 42°C and exposed in the dark for 48 hours at 4°C in light proof boxes containing drierite. Slides were developed for three minutes in Kodak® D19 developer (32 g/l of water), rinsed in water, fixed in Kodak® fixer for 5 minutes, rinsed in water, air dried and mounted with Aqua-Mount (Lerner Laboratories, Pittsburgh, PA). Slides were screened at 25x total magnification. A single clone, CG-18, was isolated by SIB selection as described (McCormick, 1987). DS-DNA was sequenced with a Sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer. Nucleotide and peptide sequence analysis were performed with GCG programs (Genetics Computer group, Madison, WI).

#### Isolation of the human Y5 homolog

Using rat oligonucleotide primers in TM 3 (sense primer; position 484-509 in SEQ ID NO:1) and in TM 6 (antisense primer; position 1219-1243 in SEQ ID NO: 1), a human hippocampal cDNA library has been screened using the polymerase chain reaction. 1  $\mu$ l ( $4 \times 10^6$  bacteria) of each of 450 amplified pools containing each »5000 independent clones and representing a total of  $2.2 \times 10^6$  was subjected directly to 40 cycles of PCR and the resulting products analyzed by agarose gel electrophoresis. One of three positive pools was analyzed further and by sib selection a single cDNA clone was isolated and characterized. This cDNA turned out to be full length and in the correct orientation for expression. DS-DNA was sequenced with a sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer.

#### Cell Culture

COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37°C, 5% CO<sub>2</sub>. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO<sub>2</sub>. Stock plates of 293 cells were trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LMT(k)- cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO<sub>2</sub>. Stock plates of COS-7 cells were trypsinized and split 1:10 every 3-4 days.

#### Stable Transfection

Human Y5 and rat Y5 receptors were co-transfected with a G-418 resistant gene into mouse fibroblast LMT(k)- cells by a calcium phosphate transfection method (Cullen, B.



(1987). Use of eukaryotic expression technology in the functional analysis of cloned genes. Methods Enzymol. 152: 685-704). Stably transfected cells were selected with G-418.

## EXPERIMENTAL RESULTS

### cDNA Cloning

In order to clone a rat hypothalamic "atypical" NPY receptor subtype, applicants used an expression cloning strategy in COS-7 cells (Gearing et al, 1989; Kluxen, F.W., Bruns, C. and Lubbert H. (1992). Expression cloning of a rat brain somatostatin receptor cDNA. Proc. Natl. Acad. Sci. USA 89, 4618-4622; Kieffer, B., Befort, K., Gaveriaux-Ruff, C. and Hirth, C.G. (1992). The

$\delta$ -opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. Proc. natl. Acad. Sci. USA 89, 12048-12052). This strategy was chosen for its extreme sensitivity since it allows detection of a single "receptor positive" cell by direct microscopic autoradiography. Since the "atypical" receptor has only been described in feeding behavior studies involving injection of NPY and NPY related ligands in rat hypothalamus (see introduction), applicants first examined its binding profile by running competitive displacement studies of  $^{125}\text{I}$ -PYY and  $^{125}\text{I}$ -PYY<sub>3-36</sub> on membranes prepared from rat hypothalamus. The competitive displacement data indicate: 1) Human PP is able to displace 20% of the bound  $^{125}\text{I}$ -PYY with an  $\text{IC}_{50}$  of 11 nM (Fig. 1 and Table 2). As can be seen in table 5, this value does not fit with the isolated rat Y1, Y2 and Y4 clones and could therefore correspond to another NPY/PYY receptor subtype. 2) [Leu<sub>31</sub>, Pro<sub>34</sub>] NPY (a Y1 specific ligand) is able to displace with high affinity ( $\text{IC}_{50}$  of 0.38) 27% of the bound  $^{125}\text{I}$ -PYY<sub>3-36</sub> ligand (a Y2 specific ligand) (Fig. 2 and table 2). These data provide the first evidence based on a binding assay that rat hypothalamic membranes could carry an NPY receptor subtype with a mixed Y1/Y2 pharmacology (referred to as the "atypical" subtype) which fits with the pharmacology defined in feeding behavior studies.

TABLE 2: Pharmacological profile of the rat hypothalamus.

Binding data reflect competitive displacement of  $^{125}\text{I}$ -PYY and  $^{125}\text{I}$ -PYY<sub>3-36</sub> from rat hypothalamic membranes. Peptides were tested at concentrations ranging from 0.001 nM to 100 nM unless noted. The  $\text{IC}_{50}$  value corresponding to 50% displacement, and the

percentage of displacement relative to that produced by 300 nM human NPY, were determined by nonlinear regression analysis. Data shown are representative of at least two independent experiments.

TABLE 2

Peptide	IC <sub>50</sub> Values, nM (% NPY-produced displacement)	
	<sup>125</sup> I-PYY	<sup>125</sup> I-PYY <sub>3-36</sub>
human NPY	0.82 (100%)	1.5 (100%)
human NPY <sub>2-36</sub>	2.3 (100%)	1.2 (100%)
human [Leu <sup>31</sup> ,Pro <sup>34</sup> ]NPY	0.21 (44%) 340 (56%)	0.38 (27%) 250 (73%)
human PYY	1.3 (100%)	0.29 (100%)
human PP	11 (20%)	untested

Based on the above data, a rat hypothalamic cDNA library of  $3 \times 10^6$  independent recombinants with a 2.7 kb average insert size was fractionated into 450 pools of »7500 independent clones. All pools were tested in a binding assay with <sup>125</sup>I-PYY as described (Y2 patent). Seven pools gave rise to positive cells in the screening assay (# 81, 92, 147, 246, 254, 290, 312). Since Y1, Y2, Y4 and Y5 receptor subtypes (by PCR or binding analysis) are expressed in rat hypothalamus, applicants analyzed the DNA of positive pools by PCR with rat Y1, Y2 and Y4 specific primers. Pools # 147, 246, 254 and 312 turned out to contain cDNAs encoding a Y1 receptor, pool # 290 turned out to encode a Y2 subtype, but pools # 81 and 92 were negative by PCR analysis for Y1, Y2 and Y4 and therefore likely contained a cDNA encoding a new rat hypothalamic NPY receptor (Y5). Pools # 81 and 92 later turned out to contain an identical NPY receptor cDNA. Pool 92 was subjected to sib selection as described until a single clone was isolated (designated CG-18).

The isolated clone carries a 2.8 kb cDNA. This cDNA contains an open reading frame between nucleotides 779 and 2146 that encodes a 456 amino acid protein. The long 5' untranslated region could be involved in the regulation of translation efficiency or mRNA stability. The flanking sequence around the putative initiation codon does not conform to the Kozak consensus sequence for optimal translation initiation (Kozak, M. (1989). The scanning model for translation: an update. J. Cell Biol. 108, 229-241; Kozak, M. (1991). Structural features in eukaryotic mRNAs that modulate the initiation of translation. J. Biol. Chem. 266, 19867-19870). The hydrophobicity plot displayed seven hydrophobic, putative membrane spanning regions which makes the rat hypothalamic Y5 receptor a member of the G-protein coupled superfamily. The nucleotide and deduced amino acid sequences are shown in SEQ ID NOS: 1 and 2, respectively.

Localization studies show that the Y5 mRNA is present in several areas of the rat hippocampus. Assuming a comparable localization in human brain, applicants screened a human hippocampal cDNA library with rat oligonucleotide primers which were shown to yield a DNA band of the expected size in a PCR reaction run on human hippocampal cDNA. Using this PCR screening strategy (Gerald et al, 1994, submitted for publication), three positive pools were identified. One of these pools was analyzed further, and an isolated clone was purified by sib selection. The isolated clone (CG-19) turned out to contain a full length cDNA cloned in the correct orientation for functional expression (see below). The human Y5 nucleotide and deduced amino acid sequences are shown in SEQ ID NOS 3 and 4, respectively. When compared to the rat Y5 receptor the human sequence shows 84.1% nucleotide identity and 87.2% amino acid identity. The rat protein sequence is one amino acid longer at the very end of both amino and carboxy tails of the receptor when compared to the rat. Both pharmacological profiles and functional characteristics of the rat and human Y5 receptor subtype homologs may be expected to match closely.

When the human and rat Y5 receptor sequences were compared to other NPY receptor subtypes or to other human G protein-coupled receptor subtypes, both overall and transmembrane domain identities are very low, showing that the Y5 receptor genes are not closely related to any other previously characterized cDNAs.

The compounds according to the present invention and their pharmaceutically acceptable salts have proven to exhibit pronounced and selective affinity to the Y5 receptor subtype

(shown in Y5 binding test) and in vitro and in vivo antagonistic properties. These properties are shown in vitro by their ability to inhibit NPY-induced calcium increase in stable transfected cells expressing the Y5 receptor and in vivo by their ability to inhibit food intake induced by intracerebroventricular application of NPY or 24 h food deprivation in conscious rats.

#### Binding experiments

The selective affinity of the compounds according to the present invention to the Y5 receptor is detected in a Y5 binding assay using LM(tk-)-h-NPY5-7 cells which stably express the human NPY Y5 receptor or HEK-293 cells stably expressing the rat NPY Y5 receptor.

The following buffers are used for the preparation of membranes and for binding assay:

a) buffer 1 (homogenisation buffer, pH 7.7 at 4°C) contains Tris-HCl [FLUKA, Buchs, Switzerland] (20 mM) and ethylenediamine tetraacetate (EDTA) [FLUKA, Buchs, Switzerland] (5 mM); b) buffer 2 (suspension buffer, pH: 7.4 at room temperature) contains N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) [Boehringer Mannheim, Germany] (20 mM), NaCl (10 mM), CaCl<sub>2</sub> (1.26 mM), MgSO<sub>4</sub> (0.81 mM) and KH<sub>2</sub>PO<sub>4</sub> (0.22 mM); buffer 3 (binding buffer, pH 7.4 at room temperature) contains HEPES (20 mM), NaCl (10 mM), CaCl<sub>2</sub> (1.26 mM), MgSO<sub>4</sub> (0.81 mM), KH<sub>2</sub>PO<sub>4</sub> (0.22 mM) and 1 mg/ml bovine serum albumin [FLUKA].

Cells are washed in phosphate buffered saline and harvested using a rubber policeman. The cells are homogenised using a Polytron homogeniser (3 bursts of 8 seconds) in ice-cold hypotonic buffer (buffer 1, pH 7.7 at 4°C). The homogenate is centrifuged at 32,000 x g for 20 min at 4°C. The pellets are resuspended in the same buffer and recentrifuged. The final pellets are suspended in buffer 2. Protein concentration is measured by the method of Bradford using the Pierce reagent [PIERCE, Rockford, USA], with bovine serum albumin as standard. The crude membrane preparation is aliquoted, flash-frozen in liquid nitrogen and stored at -80°C. Before use, 0.1% (1 mg/ml) bovine serum albumin is added.

<sup>125</sup>I-[Pro<sup>34</sup>]hPYY (60 pM, Anawa, Wangen, Switzerland) dissolved in buffer 3 is used as radioligand. All test compounds are dissolved in dimethyl sulfoxide (DMSO) at 10<sup>-2</sup> M and diluted to 10<sup>-3</sup> M in buffer 3. Subsequent dilutions are in buffer 3 plus 10% DMSO. Incubations are performed in Millipore Multiscreen FC filter plates [Millipore, Bedford, USA]. The filters in each well are pretreated with 2% polyethyleneimine for 30 min and rinsed once with 300 microL buffer 3 before use. The following are pipetted into each well: 20 microL

buffer 3, 25 microL  $^{125}\text{I}$ -[Pro $^{34}$ ]hPYY [SAXON, Hannover, Germany] (600 pM); 25 microL test compound (or binding buffer for the controls); 180 microL crude membrane suspension (approximately 5 microg protein). Incubations are performed at room temperature for 2h. Non-specific binding is defined as the binding remaining in the presence of 1 microM [Pro $^{34}$ ]hPYY. The incubations are terminated by rapid filtration and washing four times with 300microL phosphate buffered saline. The filters are removed from the wells, placed into plastic tubes and assayed for radioactivity in a gamma counter [Gammamaster, WALLAC, Finland].

The IC<sub>50</sub> values of the compounds according to this invention at the human Y5 receptor range especially between about 0.1 nM and about 10 microM. Representatives are; for example, the final products of working examples 53, 54, 55, and 88, for which following IC<sub>50</sub> values [ $\mu\text{M/L}$ ] were determined: 0.0023 (Ex. 53); 0.018 (Ex. 54); 0.0017 (Ex. 55); 0.0077 (Ex. 88).

#### Measurements of calcium transient

For the determination of in vitro antagonistic properties of the compounds according to the present invention, stably transfected LM(tk-)-hY5-7 cells are used in which a NPY-induced calcium transient is measured as described below. Cells are harvested in a medium containing EDTA (0.5 mM) and phosphate buffered saline (PBS). Cells are then washed in phosphate buffered saline solution and loaded for 90 min at room temperature and pH 7.4 with 10 microM FLUO-AM (fluoro-3-acetoxy methylester, supplemented with pluronic acid as suggested by the manufacturer, Molecular Probes Inc., Eugene, Oregon, USA) in a cell culture buffer of the following composition (NaCl 120 mM, MgCl<sub>2</sub> 1 mM, KCl 5.4 mM, NaH<sub>2</sub>PO<sub>4</sub> 0.33 mM, glucose 11 mM, taurine 5 mM, pyruvate 2 mM, glutamine 1.5 mM HEPES 10 mM, insulin 10 U/l, BSA 0.1% at for 90 min at room temperature. After centrifugation the cells are resuspended in the cell culture buffer at a concentration of 3-4 million cells/ml and supplemented with 200 microM sulfinpyrazone.

Calcium transients are measured at room temperature in a milliliter plate using a Cytofluor 2350 (Millipore) with wavelength settings at 485 nm for excitation and 530 nm for emission. 180 microL of cells suspension are preincubated in the presence of various amounts of compounds dissolved in 2 microL DMSO in triplicates ( or 2 microL DMSO for the controls) for 5 min and then NPY is added at a final concentration of 100 nM. The compound

concentrations giving 50% inhibition of the maximum of the Ca transients are then calculated.

In this cell system, NPY induces Ca transients with an EC<sub>50</sub> of 50 nM. The data are analyzed using a Microsoft Excel software. The concentrations which cause a 50% inhibition of the initial control values are given as IC<sub>50</sub> values. The IC<sub>50</sub> values are determined for the compounds according to the present invention and their pharmaceutically acceptable salts.

The property of the compounds according to the present invention and their pharmaceutically acceptable salts to inhibit NPY-induced increase intracellular calcium indicates their antagonistic properties with IC<sub>50</sub> values ranging especially between about 0.1 nM and about 10 microM.

#### Measurements of NPY-induced food intake in conscious rats

In addition this antagonistic property of the Y<sub>5</sub> receptor subtype is also observed in-vivo in conscious rats by their ability to inhibit NPY-induced food intake. For these determinations food intake is measured in normal satiated rats after intracerebroventricular application (i.c.v.) of neuropeptide Y [BACHEM, Feinchemikalien, Bubendorf, Switzerland] in the presence or absence of the compounds according to the present invention. Male Sprague-Dawley rats weighing 180-220 g are used for all experiments. They are individually housed in stainless steel cages and maintained on a 11:13 h light-dark schedule (lights off at 1800 h) under controlled temperature (21-23 °C) at all times. Water and food (NAFAG lab chow pellets) [NAFAG, Gossau, Switzerland] are available ad libitum.

Under pentobarbital [ VETERINARIA AB, Zürich, Switzerland] anesthesia, all rats are implanted with a stainless steel guide cannula targeted at the right lateral ventricle. Stereotaxic coordinates, with the incisor bar set -2.0 mm below interaural line, are : -0.8 mm anterior and +1.3 mm lateral to bregma. The guide cannula is placed on the dura. Injection cannulas extended the guide cannulas -3.8 mm ventrally to the skull surface. Animals are allowed at least 4 days of recovery postoperatively before being used in the experiments.

Cannula placement is checked postoperatively by testing all rats for their drinking response to a 50 ng intracerebroventricular (icv) injection of angiotensin II . Only rats which drink at least 2.5 ml of water within 30 min after angiotensin II injection are used in the feeding studies. Injections are made in the morning 2 hours after light onset. Peptides are injected in artificial cerebrospinal fluid (ACSF) [FLUKA, Buchs, Switzerland] in a volume of 5 µl. The ACSF contains NaCl 124 mM, KCl 3.75 mM, CaCl<sub>2</sub> 2.5 mM, MgSO<sub>4</sub> 2.0 mM, KH<sub>4</sub>PO<sub>4</sub> 0.22

mM, NaHCO<sub>3</sub> 26 mM and glucose 10 mM. NPY (300 pmole) is administered by the intracerebroventricular route 10-60 minutes after administration of compounds or vehicle DMSO/water (10%,v/v) or cremophor/water (20%,v/v) [SIGMA, Buchs, Switzerland].

Food intake is measured by placing preweighed pellets into the cages at the time of NPY injection. Pellets are removed from the cage subsequently at each time point indicated in the figures and replaced with a new set of preweighed pellets.

All results are presented as means  $\pm$ SEM. Statistical analysis is performed by analysis of variance using Student-Newman-Keuls test.

The compounds according to the present invention inhibit NPY-induced food intake in rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

#### Measurements of food intake in 24 hours food deprived rats

Based on the observation that food deprivation induces an increase in the hypothalamic NPY levels, it is assumed that NPY mediates food intake induced by food deprivation. Thus, the compounds according to the present invention are also tested in rats after 24 hours food deprivation. These experiments are conducted with male Sprague-Dawley (CIBA-GEIGY AG, Sisseln, Switzerland) rats weighing between 220 and 250 g. The animals are housed in individual cages for the duration of the study and allowed free access to normal food together with tap water. The animals are maintained in room with a 12 h light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the individual cages the rats undergo a 2-4 days equilibration period, during which they are habituated to their new environment and to eating a powdered or pellet diet [NAFAG, Gossau, Switzerland]. At the end of the equilibration period, food is removed from the animals for 24 hours starting at 8.00 a.m. At the end of the fasting period the animals are injected intraperitoneally, intravenously or orally either with the compounds according to the present invention or an equivalent volume of vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v) and 10-60 min later the food is returned to them. Food intake at various time periods is monitored over the following 24 hour period. Inhibition of food intake by the compounds according to the present invention is given in percentage of the respective control vehicle-treated rats.

The compounds according to the present invention inhibit food intake in this food deprived rat model in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal,

subcutaneous or intravenous administration. Representatives are, for example, the final products of working examples 53, 55 and 88, for which an inhibition of food intake of 96% or 87% or 92%, respectively, versus the respective control vehicle-treated animals after i.p. application of 30 mg/kg was determined.

#### Measurements of food intake in obese Zucker rats

The antiobesity efficacy of the compounds according to the present invention can also be shown in Zucker obese rats, an art-known animal model of obesity. These studies are conducted with male Zucker fatty rats (fa/fa) [HARLAN CPB, Austerlitz, NL] weighing between 480 and 500 g. Animals are individually housed in metabolism cages for the duration of the study and allowed free access to powdered food together with tap water. The animals are maintained in a room with a 12 hour light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the metabolism cages the rats undergo a 6 day equilibration period, during which they are habituated to their new environment and to eating a powdered diet. At the end of the equilibration period, food intake during the light and dark phases is determined. After a 3 day control period, the animals are treated with the compounds according to the present invention or vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v).

The compounds according to the present invention inhibit food intake in Zucker obese rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

The above experiments clearly demonstrate that the Y5 receptor subtype is the primary mediator of NPY-induced feeding and that corresponding antagonists can be used for the treatment of obesity and related disorders [*Nature*, Vol. 382, 168-171 (1996)].

The compounds according to the present invention can inhibit food intake induced either by intracerebroventricular application of NPY or by food deprivation or as well as spontaneous eating in the Zucker obese rat. Thus, the compounds according to the present invention can especially be used for the prophylaxis and treatment of disorders or diseases associated with the Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine,



sleep disturbance, and pain and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The compounds according to the present invention act as antagonists of neuropeptide Y (NPY) binding at the Y5 receptor subtype. By virtue of their Y5 receptor antagonistic property, the compounds of the formula (I) and their pharmaceutically acceptable salts can therefore be used, for example, as pharmaceutical active ingredients in pharmaceutical compositions which are employed, for example, for the prophylaxis and treatment of diseases and disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to a method of treatment of diseases and disorders associated with NPY Y5 receptor subtype, especially in the prophylaxis and treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea, comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the manufacture of a pharmaceutical composition for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes,

dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyslipidemia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof, e.g. in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R<sub>2</sub> represents

(i) hydrogen, halogen, lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by substituted amino, by lower alkoxy-carbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, or by substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxy-carbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is di-

substituted by lower alkylene (which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>) or which is disubstituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X<sub>3</sub>(X<sub>4</sub>)(X<sub>5</sub>) wherein, (a) if X<sub>3</sub> is -CH-, X<sub>4</sub> together with X<sub>5</sub> represent a structural element of formula -X<sub>6</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-X<sub>6</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>r</sub>-, or -(CH<sub>2</sub>)<sub>s</sub>-X<sub>6</sub>-CO-(CH<sub>2</sub>)<sub>t</sub>-; or, (b) if X<sub>3</sub> is -N-, X<sub>4</sub> together with X<sub>5</sub> represent a structural element of formula -CO-(CH<sub>2</sub>)<sub>u</sub>-; [X<sub>6</sub> being -CH<sub>2</sub>-, -N(R<sub>1</sub>)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X<sub>4</sub> is different from -CH<sub>2</sub>-];

X<sub>1</sub> represents C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, or oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene;

X<sub>2</sub> represents -O-, -S(O)<sub>n</sub>- or a group of the formula -N(R<sub>4</sub>)-;

R<sub>3</sub> and R<sub>4</sub>, independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or  
 (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, substituted carbamoyl, and -S(O)<sub>n</sub>-R;

R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, or NR<sub>0</sub>] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;  
 (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolinyl, or quinazolinyl;

wherein, in each case, the amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R<sub>2</sub> represents

- (i) hydrogen, halogen, lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by substituted amino, by lower alkoxy-carbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, or by substituted carbamoyl;
- (ii) amino or substituted amino;
- (iii) hydroxy, lower alkoxy, lower alkenyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxy-carbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl-oxy, or N-substituted aminocarbonyl-oxy;
- (iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (v) N-substituted carbamoyl;
- (vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

X<sub>1</sub> represents C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, or oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene;

X<sub>2</sub> represents -O-, -S(O)<sub>n</sub>- or a group of the formula -N(R<sub>4</sub>)-;

R<sub>3</sub> and R<sub>4</sub>, independently of one another, represent

- (i) hydrogen, lower alkyl, lower alkenyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, substituted carbamoyl, and -S(O)<sub>n</sub>-R;

R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, or NR<sub>0</sub>] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

- (i) halogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iv) amino, substituted amino;
- (v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolinyl, or quinazolinyl;

wherein, in each case, the amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R<sub>2</sub> represents

- (i) hydrogen, halogen, lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by substituted amino, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, or by substituted carbamoyl;
- (ii) amino or substituted amino;
- (iii) hydroxy, lower alkoxy, lower alkenyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;
- (iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (v) N-substituted carbamoyl;
- (vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

X<sub>1</sub> represents C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, or oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene;

X<sub>2</sub> represents -O-, -S(O)<sub>n</sub>- or a group of the formula -N(R<sub>4</sub>)-;

R<sub>3</sub> and R<sub>4</sub>, independently of one another, represent

- (i) hydrogen, lower alkyl, lower alkenyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino,

substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, substituted carbamoyl, and  $-S(O)_n-R$ ;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ , or  $NR_0$ ] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

- (i) halogen, lower alkyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3-C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iv) amino, substituted amino;
- (v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, is derived from phenyl, naphthyl or pyridyl;

wherein, in each case, the amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by  $C_3-C_8$ -cycloalkyl, by  $C_3-C_8$ -cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O,  $S(O)_n$  or  $NR_0$ ] or is di-substituted by lower alkylene which is condensed at two adjacent



carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by  $-\text{CO}(\text{O})_v\text{R}$  and the integer  $v$  is 0 or 1;

wherein, in each case, the integer  $n$  is 0, 1 or 2;

wherein, in each case,  $\text{R}_0$  represents hydrogen or lower alkyl;

wherein, in each case,  $\text{R}$  represents hydrogen, lower alkyl,  $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ , (carbocyclic or heterocyclic) aryl-lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

$\text{alk}_1$  and  $\text{alk}_2$ , independently of one another, represent a single bond or lower alkylene;

$\text{R}_1$  represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

$\text{R}_2$  represents

(i) hydrogen;

(ii) amino, amino which is monosubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkyl or by  $\text{C}_2\text{-C}_6\text{-alkylene}$  or amino which is monosubstituted by  $-\text{CO}-\text{O}-\text{R}$  and  $\text{R}$  being lower alkyl;

(iii) lower alkoxy-carbonyl-oxy or (carbocyclic or heterocyclic) aryl-carbonyl-oxy;

(vi) a group selected from  $-\text{CH}(\text{OH})-\text{R}$  and  $\text{R}$  being hydrogen, lower alkyl or phenyl-lower alkyl,  $-\text{CO}-\text{R}$  and  $\text{R}$  being hydrogen or lower alkyl,  $-\text{NR}_1-\text{CO}-\text{O}-\text{R}$  and  $\text{R}_1$  being hydrogen and  $\text{R}$  being lower alkyl,  $-\text{NR}_1-\text{CO}-\text{R}$  and  $\text{R}_1$  being hydrogen or lower alkyl and  $\text{R}$  being lower alkyl, phenyl or lower alkoxy-lower alkyl,  $-\text{NR}_1-\text{SO}_2-\text{R}$  and  $\text{R}_1$  being hydrogen or lower alkyl and  $\text{R}$  being lower alkyl, phenyl-lower alkyl, phenyl or naphthyl,  $-\text{NR}_1-\text{SO}_2-\text{NR}_1-\text{R}$  and  $\text{R}_1$  being hydrogen and  $-\text{N}(\text{R}_1)(\text{R})$  being amino disubstituted by lower alkyl or by  $\text{C}_2\text{-C}_6\text{-alkylene}$  or being morpholino, piperazino or 4-lower alkyl-piperazino,  $-\text{SO}_2-\text{R}$  and  $\text{R}$  being lower alkyl or phenyl;

$\text{X}_1$  represents  $\text{C}_3\text{-C}_8\text{-cycloalkylene}$ , especially cyclohexylene;

$\text{X}_2$  represents  $-\text{O}-$  and  $\text{R}_3$  is hydrogen; or

$\text{X}_2$  represents a group of the formula  $-\text{N}(\text{R}_4)-$  and  $\text{R}_4$  is hydrogen or lower alkyl; and

$\text{R}_3$  represents

(i) hydrogen, lower alkyl,  $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ ,  $\text{C}_3\text{-C}_8\text{-cycloalkyl-lower alkyl}$ , or phenyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: hydroxy, lower alkoxy, hydroxy-lower alkoxy, amino, amino monosubstituted by lower

alkoxycarbonyl or disubstituted by lower alkyl, morpholino, piperazino, 4-lower alkyl-piperazino, 4-lower alkoxycarbonyl-piperazino and carbamoyl disubstituted by lower alkyl; or  
X<sub>2</sub> and R<sub>3</sub> together represent morpholino or 4-lower alkyl-piperazino;

wherein, in each case, any aryl moiety as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, nitro, lower alkyl, phenyl, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy and lower alkoxycarbonyl.

The invention relates especially to a compound of formula (I) or a salt or tautomer thereof in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen or lower alkyl;

R<sub>2</sub> represents

hydrogen, lower alkoxycarbonyl-oxy, amino, amino disubstituted by C<sub>3</sub>-C<sub>6</sub>-alkylene, a group selected from -NR<sub>1</sub>-CO-O-R [R being lower alkyl and R<sub>1</sub> being hydrogen], -NR<sub>1</sub>-CO-R [R being lower alkyl, hydroxy-lower alkyl, phenyl-lower alkyl, or phenyl and R<sub>1</sub> being hydrogen], -NR<sub>1</sub>-SO<sub>2</sub>-R [R being lower alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, phenyl-lower alkyl, naphthyl-lower alkyl, phenyl, naphthyl, or quinoliny and R<sub>1</sub> being hydrogen and the aryl radicals being unsubstituted or substituted by lower alkyl, lower alkoxy, lower alkoxycarbonyl], -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R [R<sub>1</sub> being hydrogen, and the group-N(R)(R<sub>1</sub>) being di-lower alkylamino, 1-piperidino, 1-piperazino, 4-lower alkyl-1-piperazino, or 4-morpholino],  
-SO<sub>2</sub>-R [R being lower alkyl], or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R and R<sub>1</sub> being each lower alkyl];

X<sub>1</sub> represents C<sub>3</sub>-C<sub>6</sub>-cycloalkylene or C<sub>3</sub>-C<sub>6</sub>-cycloalkylidene;

X<sub>2</sub> represents O and R<sub>3</sub> represents hydrogen; or

X<sub>2</sub> represents a group of the formula -N(R<sub>4</sub>)-; and

R<sub>3</sub> represents hydrogen, lower alkyl, lower alkyl substituted by hydroxy, lower alkoxy, hydroxy-lower alkoxy, di-lower alkylamino, or phenyl which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

R<sub>4</sub> represents hydrogen or lower alkyl;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, lower alkyl, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, di-lower alkylamino, and phenyl-amino.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or C<sub>1</sub>-C<sub>3</sub>-alkylene;

R<sub>1</sub> represents hydrogen;

R<sub>2</sub> represents

hydrogen, lower alkoxy, carbonyl-oxy, amino, amino di-substituted by C<sub>3</sub>-C<sub>6</sub>-alkylene, a group selected from -NR<sub>1</sub>-CO-R [R being lower alkyl, phenyl-lower alkyl, or phenyl and R<sub>1</sub> being hydrogen], -NR<sub>1</sub>-CO-O-R [R being lower alkyl], -NR<sub>1</sub>-SO<sub>2</sub>-R [R being lower alkyl, phenyl-lower alkyl, phenyl, naphthyl, or quinolyl and R<sub>1</sub> being hydrogen and phenyl being unsubstituted or substituted by lower alkyl, lower alkoxy, lower alkoxy-carbonyl], -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R [R<sub>1</sub> being hydrogen, and the group-N(R)(R<sub>1</sub>) being di-lower alkylamino], -SO<sub>2</sub>-R [R being lower alkyl], or -SO<sub>2</sub>-NR<sub>1</sub>-R, [R and R<sub>1</sub> being each lower alkyl];

X<sub>1</sub> represents C<sub>3</sub>-C<sub>6</sub>-cycloalkylene, especially 1,3-cyclopentylene, 1,3-, or 1,4-cycloalkylene;

X<sub>2</sub> represents O and R<sub>3</sub> represents hydrogen; or

X<sub>2</sub> represents a group of the formula -N(R<sub>4</sub>)-; and

R<sub>3</sub> represents hydrogen, lower alkyl, or phenyl which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

R<sub>4</sub> represents hydrogen;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen or lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk<sub>1</sub> and alk<sub>2</sub> independently of one another, represent a single bond or methylene;

R<sub>1</sub> is hydrogen;

X<sub>1</sub> is 1,4-cyclohexylene;

X<sub>2</sub> is -O-; R<sub>2</sub> is -NH-SO<sub>2</sub>-R and R being naphthyl; and R<sub>3</sub> is hydrogen; or

X<sub>2</sub> is -NH-;

R<sub>2</sub> represents -NH-SO<sub>2</sub>-R and R is phenyl substituted by halogen, especially 4-chloro-phenyl, or naphthyl; and R<sub>3</sub> represents hydrogen, C<sub>1</sub>-C<sub>4</sub>-alkyl which substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl-amino or by C<sub>1</sub>-C<sub>4</sub>-alkyl-amino-carbonyl or by C<sub>5</sub>-C<sub>5</sub>-alkylene; or

$R_2$  represents  $C_1$ - $C_4$ -alkylamino, such as methylamino,  $C_1$ - $C_4$ -alkoxycarbonyl-amino, such as tert-butoxycarbonyl-amino,  $-NH-SO_2-R$  and  $R$  being phenyl substituted by  $C_1$ - $C_4$ -alkyl, such as 4-methyl-phenyl, or  $C_1$ - $C_4$ -alkyl, such as methyl, or is  $NH-SO_2-N(R_1)(R)$  and  $R_1$  and  $R$  each being  $C_1$ - $C_4$ -alkyl, such as methyl or ethyl; and  $R_3$  represents hydrogen, phenyl or phenyl which is substituted by halogen, such as 4-fluoro- or 4-chloro-phenyl; wherein the benzo ring A is unsubstituted or substituted by  $C_1$ - $C_4$ -alkoxy, such as methoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

$X_1$  represents 1,3- or 1,4-cyclohexylene;

$X_2$  represents a group of the formula  $-N(R_4)-$ ;

$R_1$  represents hydrogen;

$R_3$  represents hydrogen;

$R_4$  represents hydrogen;

$alk_1$  and  $alk_2$  each represent a single bond; and  $R_2$  represents hydrogen; or

$alk_1$  represents methylene and  $alk_2$  represents  $C_1$ - $C_2$ -alkylene; and  $R_2$  represents a group  $-NR_1-SO_2-R$  [ $R$  being naphthyl, especially 1- or 2-naphthyl];

wherein the benzo ring A is unsubstituted or substituted by  $C_1$ - $C_4$ -alkoxy, especially methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

$alk_1$  and  $alk_2$  each represent methylene,

$X_1$  represents 1,4-cyclohexylene;

$X_2$  represents a group of the formula  $-NH-$ ;

$R_2$  represents amino which is disubstituted by  $C_4$ - $C_5$ -alkylene, such as 1-piperidino; and  $R_3$  represents phenyl which is substituted by halogen, especially 4-chloro-phenyl; or

$R_2$  represents  $-NH-SO_2-R$  and  $R$  being naphthyl; and  $R_3$  represents hydrogen,  $C_1$ - $C_4$ -alkyl which is substituted by di-  $C_1$ - $C_4$ -alkylamino or by 4- $C_1$ - $C_4$ -alkyl-piperazino, such as 4-methyl-piperazino;

wherein the benzo ring A is unsubstituted or substituted by  $C_1$ - $C_4$ -alkoxy, especially methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

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alk<sub>1</sub> and alk<sub>2</sub> each represent methylene,

X<sub>1</sub> represents 1,4-cyclohexylene;

X<sub>2</sub> represents a group of the formula -N(R<sub>4</sub>)-;

R<sub>1</sub>, R<sub>3</sub>, and R<sub>4</sub> each represents hydrogen;

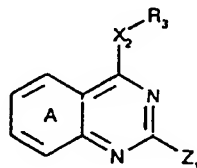
R<sub>2</sub> represents -NH-SO<sub>2</sub>-R and R represents 1- or 2-naphthyl; and

wherein the benzo ring A is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy, especially methoxy, in position 8 of the quinazoline ring.

The invention relates in particular to the novel compounds shown in the examples and to the modes of preparation described therein.

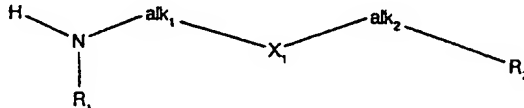
The invention relates to processes for the preparation of the compounds according to the invention. The preparation of new compounds of the formula (I) and their salts comprises, for example,

(a) reacting a compound of formula (IIa) or a salt thereof



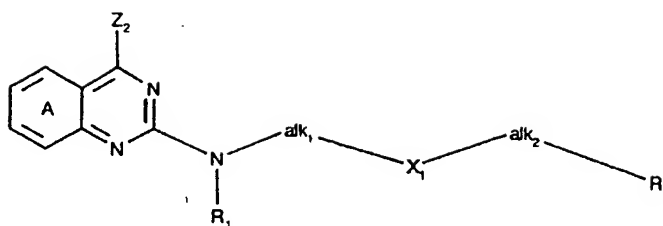
in which Z<sub>1</sub> represents a leaving group,

with a compound of formula (IIb) or a salt thereof



or

(b) reacting a compound of formula (IIIa) or a salt thereof



in which  $Z_2$  is a leaving group

with a compound of formula  $H-X_2-R_3$  (IIIb) or a salt thereof,

and, if desired, converting a compound (I) obtainable according to the process or in another manner, in free form or in salt form, into another compound (I), separating a mixture of isomers obtainable according to the process and isolating the desired isomer and/or converting a free compound (I) obtainable according to the process into a salt or converting a salt of a compound (I) obtainable according to the process into the free compound (I) or into another salt.

The reactions described above and below in the variants are carried out in a manner known per se, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about  $-80^{\circ}\text{C}$  up to the boiling point of the reaction medium, preferably from about  $-10^{\circ}$  to about  $+200^{\circ}\text{C}$ , and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions. The person skilled in the pertinent art is especially referred to the methods as outlined in the working examples based upon which the person skilled in the art is enabled to carry out the manufacture of the compounds of formula (I).

Salts of starting materials which have at least one basic centre, for example of the formula IIIb, are appropriate acid addition salts, while salts of starting materials which have an acidic group, for example of the formula (IIb), are present as salts with bases, in each case as mentioned above in connection with corresponding salts of the formula (I).

A leaving group  $Z_1$  or  $Z_2$ , respectively, is, for example, reactive esterified hydroxy, or is  $R'-S(O)_u-$  [the integer  $u$  being 0, 1 or 2 and  $R'$  being lower alkyl, halo-lower alkyl or aryl, such as methyl, trifluoromethyl or *p*-toluyl], or is lower alkoxy.

Reactive esterified hydroxyl ( $Z_4$ ) is in particular hydroxyl esterified with a strong inorganic acid or organic sulfonic acid, for example halogen, such as fluorine, chlorine, or bromine, sulfonyloxy, such as hydroxysulfonyloxy, halosulfonyloxy, for example fluorosulfonyloxy,  $C_1$ - $C_7$ -alkane-sulfonyloxy which is unsubstituted or substituted, for example by halogen, for example methane- or trifluoromethanesulfonyloxy,  $C_5$ - $C_7$ -cycloalkanesulfonyloxy, for example cyclohexanesulfonyloxy, or benzenesulfonyloxy which is unsubstituted or substituted, for example by  $C_1$ - $C_7$ -alkyl or halogen, for example *p*-bromobenzene- or *p*-toluenesulfonyloxy. Preferred  $Z_1$  or  $Z_2$  is chloro, bromo or iodo, methanesulfonyloxy or trifluoromethanesulfonyloxy, or *p*-toluenesulfonyloxy, or methylthio or methoxy.

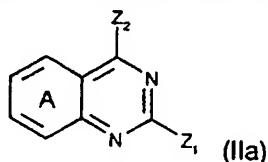
The reactions of process variants (a) and (b) are carried out, if necessary, in the presence of a base. Suitable bases are, for example, alkali metal hydroxides, hydrides, amides, alkanolates, carbonates, triphenylmethylenes, di-lower alkylamides, aminoalkylamides or lower alkylsilylamides, naphthaleneamines, lower alkylamines, basic heterocycles, ammonium hydroxides, and carbocyclic amines. Examples which may be mentioned are sodium hydroxide, sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium *tert*-butoxide, potassium carbonate, lithium triphenylmethylenide, lithium diisopropylamide, potassium 3-(aminopropyl)amide, potassium bis(trimethylsilyl)amide, dimethylaminonaphthalene, di- or triethylamine, or ethyldiisopropylamine, *N*-methylpiperidine, pyridine, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The starting material of formulae (IIa), (IIb), (IIIa), and (IIIb) is essentially known or is accessible analogously to preparation processes known per se.

The starting material of the formula (IIa) is essentially described, for example, in US Patent No. 5,064,833.

The starting material of formula (IIb) in which  $R_2$  represents N-acylated or N-alkylated amino, such as a group of formula  $-NR_1-CO-O-R$ ,  $-NR_1-CO-R$ ,  $-NR_1-CO-NR_1-R$ ,  $-NR_1-SO_2-R$ ,  $-NR_1-SO_2-NR_1-R$ , or N-substituted amino, is accessible, for example, by N-acylating or by N-alkylating, respectively, a, preferably N-protected, compound of the formula  $NH(R_1)-alk_1-X-alk_2-Z_3$  (IIc) in which  $Z_3$  represents a group which is convertible to  $R_2$ , such as amino, carboxy, or hydroxy. Conventional protecting groups may be used, for example, t-butoxycarbonyl which will be split off after the N-acylation or the N-alkylation, respectively. The starting material of formula (IIb) in which  $R_2$  represents carbamoyl or N-substituted carbamoyl, or esterified carboxy, can be manufactured starting from a compound of formula (IIc) in which  $Z_3$  represents carboxy. The esterification or amidation can be carried out in a manner known per se. Starting from a compound of formula (IIc) in which  $Z_3$  is hydroxy, corresponding etherified or esterified derivatives are accessible using etherification or esterification methods known in the art.

The starting material of formula (IIIa) is accessible, for example, by selectively converting the  $Z_2$ -group in position 4 into a group which is deactivated, for example, by selectively hydrolyzing a compound of formula (IIIc)



or a salt thereof to form a corresponding 4-hydroxy-compound ( $X_2$  being O and  $R_3$  being hydrogen) which is in the next step reacted with a compound of formula (IIb) to introduce the corresponding side chain into position 2 of the quinazoline ring. Reactivation of the 4-position, if required, for example, by reaction with a halogenating agent, such as  $POCl_3$ , leads to corresponding compounds of formula (IIIa) in which  $X_2$  is  $N(R_4)$ .



A compound according to the invention which is obtainable by the process can be converted into another compound according to the invention in a manner known per se.

A compound according to the invention containing hydroxyl can be etherified by methods known per se. The etherification can be carried out, for example, using an alcohol, such as a substituted or unsubstituted lower alkanol, or a reactive ester thereof. Suitable reactive esters of the desired alcohols are, for example, those with strong inorganic or organic acids, such as corresponding halides, sulfates, lower alkanesulfonates or substituted or unsubstituted benzenesulfonates, for example chlorides, bromides, iodides, methane-, benzene- or p-toluenesulfonates. The etherification can be carried out, for example, in the presence of a base, an alkali metal hydride, hydroxide or carbonate, or of an amine. Conversely, corresponding ethers, such as lower alkoxy compounds, can be cleaved, for example, by means of strong acids, such as mineral acids, for example the hydrohalic acids hydrobromic or hydriodic acid, which may advantageously be present in the form of pyridinium halides, or by means of Lewis acids, for example halides of elements of main group III or the corresponding sub-groups. These reactions can be carried out, if necessary, with cooling or warming, for example in a temperature range from about -20° to about 100°C, in the presence or absence of a solvent or diluent, under inert gas and/or under pressure and, if appropriate, in a closed vessel.

Compounds according to the invention containing hydroxymethyl groups can be prepared, for example, starting from compounds containing corresponding carboxyl or esterified carboxyl, corresponding compounds being reduced in a manner known per se, for example by reduction with a hydride which, if desired, may be complex, such as a hydride formed from an element of the 1st and 3rd main groups of the periodic table of the elements, for example borohydride or aluminohydride, for example lithium borohydride, lithium aluminium hydride, diisobutylaluminium hydride (an additional reduction step using alkali metal cyanoborohydride, such as sodium cyanoborohydride, may be necessary), and also diborane.

If an aromatic structural component is substituted by (lower) alkylthio (in  $S(O)_n$  -R n is 0), this can be oxidised in a customary manner to corresponding (lower) alkanesulfinyl or -sulfonyl. Suitable oxidising agents for the oxidation to the sulfoxide step are, for example, inorganic peracids, such as peracids of mineral acids, for example periodic acid or persulfuric acid, organic peracids, such as appropriate percarboxylic or persulfonic acids, for example performic, peracetic, trifluoroperacetic or perbenzoic acid or p-toluenepersulfonic acid, or mixtures of hydrogen peroxide and acids, for example a mixture of hydrogen peroxide with acetic acid.

The oxidation is commonly carried out in the presence of suitable catalysts, catalysts which can be mentioned being suitable acids, such as substituted or unsubstituted carboxylic acids, for example acetic acid or trifluoroacetic acid, or transition metal oxides, such as oxides of elements of sub-group VII, for example vanadium oxide, molybdenum oxide or tungsten oxide. The oxidation is carried out under mild conditions, for example at temperatures from about  $-50^{\circ}$  to about  $+100^{\circ}\text{C}$ .

The oxidation to the sulfone step may also be carried out appropriately at low temperatures using dinitrogen tetroxide as the catalyst in the presence of oxygen, just like the direct oxidation of (lower) alkylthio to (lower) alkanesulfonyl. However, in this case the oxidising agent is customarily employed in an excess.

If one of the variables contains amino, corresponding compounds of the formula (I), their tautomers or salts can be N-alkylated in a manner known per se; likewise, carbamoyl or radicals containing carbamoyl can be N-alkylated. The (aryl)alkylation is carried out, for example, using a reactive ester of an (aryl) $C_1$ - $C_7$ alkyl halide, for example a bromide or iodide, (aryl) $C_1$ - $C_7$ alkylsulfonate, for example methanesulfonate or p-toluenesulfonate, or a di- $C_1$ - $C_7$ alkyl sulfate, for example dimethyl sulfate, preferably under basic conditions, such as in the presence of sodium hydroxide solution or potassium hydroxide solution, and advantageously in the presence of a phase transfer catalyst, such as tetrabutylammonium bromide or benzyltrimethylammonium chloride, where,

however, stronger basic condensing agents, such as alkali metal amides, hydrides or alkoxides, for example sodium amide, sodium hydride or sodium ethoxide, may be necessary. Amino can also be acylated in a manner known per se.

In compounds of the formula (I) which contain an esterified or amidated carboxyl group as a substituent, a group of this type can be converted into a free carboxyl group, for example by means of hydrolysis, for example in the presence of a basic agent, or of an acidic agent, such as a mineral acid. Tert-butyloxycarbonyl, for example, can furthermore be converted into carboxyl, for example in a manner known per se, such as treating with trihaloacetic acid, such as trifluoroacetic acid, and benzyloxycarbonyl can be converted into carboxyl, for example by catalytic hydrogenation in the presence of a hydrogenation catalyst, for example in the manner described below.

Furthermore, in compounds of the formula (I) which contain a carboxyl group as a substituent, this can be converted into an esterified carboxyl group, for example, by treating with an alcohol, such as a lower alkanol, in the presence of a suitable esterifying agent, such as an acid reagent, for example an inorganic or organic acid or a Lewis acid, for example zinc chloride, or a condensing agent which binds water, for example a carbodiimide, such as N,N'-dicyclohexylcarbodiimide, or by treating with a diazo reagent, such as with a diazo-lower alkane, for example diazomethane. This can also be obtained if compounds of the formula (I) in which the carboxyl group is present in free form or in salt form, such as ammonium salt or metal salt form, for example alkali metal salt form, such as sodium salt or potassium salt form, are treated with a reactive ester of a (C<sub>1</sub>-C<sub>7</sub>)alkyl halide, for example methyl or ethyl bromide or iodide, or an organic sulfonic acid ester, such as an appropriate (C<sub>1</sub>-C<sub>7</sub>)alkyl ester, for example methyl or ethyl methanesulfonate or p-toluenesulfonate.

Compounds of the formula (I) which contain an esterified carboxyl group as a substituent can be transesterified into other ester compounds of the formula (I) by transesterification, for example by treating with an alcohol, customarily a higher appropriate alcohol than that of the esterified carboxyl group in the starting

material, in the presence of a suitable transesterifying agent, such as a basic agent, for example an alkali metal (C<sub>1</sub>-C<sub>7</sub>)alkanoate, (C<sub>1</sub>-C<sub>7</sub>)alkanolate or alkali metal cyanide, such as sodium acetate, sodium methoxide, sodium ethoxide, sodium tert-butoxide or sodium cyanide, or a suitable acid agent, if appropriate with removal of the resulting alcohol, for example by distillation. Appropriate, so-called activated esters of the formula (I) which contain an activated esterified carboxyl group as a substituent may also be used as starting materials (see below), and these may be converted into another ester by treating with a (C<sub>1</sub>-C<sub>7</sub>)alkanol.

In compounds of the formula (I) which contain the carboxyl group as a substituent, this can also first be converted into a reactive derivative, such as an anhydride, including a mixed anhydride, such as an acid halide, for example an acid chloride (for example by treating with a thionyl halide, for example thionyl chloride), or an anhydride using a formic acid ester, for example a (C<sub>1</sub>-C<sub>7</sub>)alkyl ester (for example by treating a salt, such as an ammonium or alkali metal salt, with a haloformic acid ester, such as a chloroformic acid ester, such as a (C<sub>1</sub>-C<sub>7</sub>)alkyl ester), or into an activated ester, such as a cyanomethyl ester, a nitrophenyl ester, for example a 4-nitrophenyl ester, or a polyhalophenyl ester, for example a pentachlorophenyl ester (for example by treating with an appropriate hydroxyl compound in the presence of a suitable condensing agent, such as N,N'-dicyclohexylcarbodiimide), and then a reactive derivative of this type can be reacted with an amine and in this way amide compounds of the formula (I) which contain an amidated carboxyl group as a substituent can be obtained. In this case, these can be obtained directly or via intermediate compounds; thus, for example, an activated ester, such as a 4-nitrophenyl ester, of a compound of the formula (I) containing a carboxyl group can first be reacted with a 1-unsubstituted imidazole and the 1-imidazolylcarbonyl compound obtained in this way brought to reaction with an amine. However, other non-activated esters, such as (C<sub>1</sub>-C<sub>7</sub>)alkyl esters of compounds of the formula (I), which contain, for example, (C<sub>2</sub>-C<sub>8</sub>)alkoxycarbonyl as a substituent, can also be brought to reaction with amines.

If an aromatic ring contains a hydrogen atom as a substituent, the latter can be replaced by a halogen atom with the aid of a halogenating agent in a customary

manner, for example brominated with bromine, hypobromic acid, acyl hypobromites or other organic bromine compounds, for example N-bromosuccinimide, N-bromoacetamide, N-bromophthalimide, pyridinium perbromide, dioxane dibromide, 1,3-dibromo-5,5-dimethylhydantoin or 2,4,4,6-tetrabromo-2,5-cyclohexanedien-1-one, or chlorinated with elemental chlorine, for example in a halogenated hydrocarbon, such as chloroform, and with cooling, for example from down to about -10° to about +100°C.

If an aromatic ring in the compounds according to the invention contains an amino group, this can be diazotized in a customary manner, for example by treating with a nitrite, for example sodium nitrite, in the presence of a suitable protonic acid, for example a mineral acid, the reaction temperature advantageously being kept below about 5°C. The diazonium group present in the salt form and obtainable in this way can be substituted by analogous processes, for example as follows: by the hydroxyl group analogously to the boiling-out of phenol in the presence of water; by an alkoxy group by treating with an appropriate alcohol, energy having to be added; by the fluorine atom analogously to the Schiemann reaction in the thermolysis of corresponding diazonium tetrafluoroborates; by the halogen atoms chlorine, bromine or iodine and also the cyano group analogously to the Sandmeyer reaction in the reaction with corresponding Cu(I) salts, initially with cooling, for example to below about 5°C, and then heating, for example to about 60° to about 150°C.

If the compounds of the formula (I) contain unsaturated radicals, such as (lower) alkenyl or (lower) alkynyl groups, these can be converted into saturated radicals in a manner known per se. Thus, for example, multiple bonds are hydrogenated by catalytic hydrogenation in the presence of hydrogenation catalysts, suitable catalysts for this purpose being, for example, nickel, such as Raney nickel, and noble metals or their derivatives, for example oxides, such as palladium or platinum oxide, which may be applied, if desired, to support materials, for example to carbon or calcium carbonate. The hydrogenation may preferably be carried out at pressures between 1 and about 100 at and at room temperature between about -80° to about 200°C, in particular between room temperature and about 100°C. The reaction is advantageously carried out in a solvent, such as

water, a lower alkanol, for example ethanol, isopropanol or n-butanol, an ether, for example dioxane, or a lower alkanecarboxylic acid, for example acetic acid.

Furthermore, in compounds of the formula (I) in which, for example, one of the aryl radicals contains halogen, such as chlorine, halogen can be replaced by reaction with a substituted or unsubstituted amine, an alcohol or a mercaptan.

The invention relates in particular to the processes described in the examples.

Salts of compounds of the formula (I) can be prepared in a manner known per se. Thus, for example, acid addition salts of compounds of the formula (I) are obtained by treating with an acid or a suitable ion exchange reagent. Salts can be converted into the free compounds in a customary manner, and acid addition salts can be converted, for example, by treating with a suitable basic agent.

Depending on the procedure and reaction conditions, the compounds according to the invention having salt-forming, in particular basic properties, can be obtained in free form or preferably in the form of salts.

In view of the close relationship between the novel compound in the free form and in the form of its salts, in the preceding text and below the free compound or its salts may correspondingly and advantageously also be understood as meaning the corresponding salts or the free compound.

The novel compounds including their salts of salt-forming compounds can also be obtained in the form of their hydrates or can include other solvents used for crystallization.

Depending on the choice of the starting materials and procedures, the novel compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, such as antipodes, or as isomer mixtures, such as racemates, diastereoisomer mixtures or racemate mixtures, depending on the number of asymmetric carbon atoms. For example, compounds of the formula (I) in which e.g. X<sub>1</sub> has an asymmetric C atom.

Racemates and diastereomer mixtures obtained can be separated into the pure isomers or racemates in a known manner on the basis of the physicochemical differences of the components, for example by fractional crystallization.

Racemates obtained may furthermore be resolved into the optical antipodes by known methods, for example by recrystallization from an optically active solvent, chromatography on chiral adsorbents, with the aid of suitable microorganisms, by cleavage with specific immobilized enzymes, via the formation of inclusion compounds, for example using chiral crown ethers, only one enantiomer being complexed, or by conversion into diastereomeric salts, for example by reaction of a basic final substance racemate with an optically active acid, such as a carboxylic acid, for example tartaric or malic acid, or sulfonic acid, for example camphorsulfonic acid, and separation of the diastereomer mixture obtained in this manner, for example on the basis of its differing solubilities, into the diastereomers from which the desired enantiomer can be liberated by the action of suitable agents. The more active enantiomer is advantageously isolated.

The invention also relates to those embodiments of the process, according to which a compound obtainable as an intermediate in any step of the process is used as a starting material and the missing steps are carried out or a starting material in the form of a derivative or salt and/or its racemates or antipodes is used or, in particular, formed under the reaction conditions.

In the process of the present invention, those starting materials are preferably used which lead to the compounds described as particularly useful at the beginning. The invention likewise relates to novel starting materials which have been specifically developed for the preparation of the compounds according to the invention, to their use and to processes for their preparation, the variables  $\text{alk}_1$ ,  $\text{alk}_2$ ,  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ ,  $\text{X}_1$  and  $\text{X}_2$  having the meanings indicated for the preferred compound groups of the formula (I) in each case.

The invention likewise relates to pharmaceutical preparations which contain the compounds according to the invention or pharmaceutically acceptable salts thereof as active ingredients, and to processes for their preparation.

The pharmaceutical preparations according to the invention which contain the compound according to the invention or pharmaceutically acceptable salts thereof are those for enteral, such as oral, furthermore rectal, and parenteral administration to (a) warm-blooded animal(s), the pharmacological active ingredient being present on its own or together with a pharmaceutically acceptable carrier. The daily dose of the active ingredient depends on the age and the individual condition and also on the manner of administration.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 80%, preferably from about 20 % to about 60 %, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

Suitable carriers are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, furthermore binders, such as starch paste, using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, such as the abovementioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate; auxiliaries are primarily glidants, flow-regulators and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Sugar-coated tablet cores are provided with suitable coatings which, if desired, are resistant to gastric juice, using, inter alia, concentrated sugar solutions which, if desired, contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide,



coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of gastric juice-resistant coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colorants or pigments, for example to identify or to indicate different doses of active ingredient, may be added to the tablets or sugar-coated tablet coatings.

Other orally utilizable pharmaceutical preparations are hard gelatin capsules, and also soft closed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The hard gelatin capsules may contain the active ingredient in the form of granules, for example in a mixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, if desired, stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it also being possible to add stabilizers.

Suitable rectally utilizable pharmaceutical preparations are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Furthermore, gelatin rectal capsules which contain a combination of the active ingredient with a base substance may also be used. Suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable preparations for parenteral administration are primarily aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and furthermore suspensions of the active ingredient, such as appropriate oily injection suspensions, using suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if necessary, also stabilizers.

The dose of the active ingredient depends on the warm-blooded animal species, the age and the individual condition and on the manner of administration. In the normal case, an approximate daily dose of about 10 mg to about 250 mg is to be estimated in the case of oral administration for a patient weighing approximately 75 kg .

The following examples illustrate the invention described above; however, they are not intended to limit its extent in any manner. Temperatures are indicated in degrees Celsius.

The following examples illustrate the invention.

Abbreviations:

HCl	hydrochloric acid
NaOH	sodium hydroxide
THF	tetrahydrofuran
min	minute(s)
h	hour(s)
m.p.	melting point
FAB-MS	Fast Atom Bombardment Mass Spectroscopy
ESI-MS	Electro-Spray Ionization Mass Spectroscopy
Rf	retention factor on a thin layer chromatography plate

Solvent systems (v/v/v):

A1:	hexanes / ethyl acetate	1:1
A2:	hexanes / ethyl acetate	19:1
A3:	hexanes / ethyl acetate	4:1
A4:	hexanes / ethyl acetate	2:1
A5:	hexanes / ethyl acetate	3:1
A6:	ethyl acetate	
A7:	toluene / ethyl acetate	1:1
A8:	hexanes / ethyl acetate	1:2
A9:	hexanes / ethyl acetate / dichloromethane	12:6:1

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A10: hexanes / ethyl acetate / dichloromethane	8:8:1
A11: hexanes / ethyl acetate	10:1
B1: dichloromethane / methanol	19:1
B2: dichloromethane / methanol	9:1
B3: dichloromethane / methanol	5:1
B4: dichloromethane / methanol	4:1
B5: dichloromethane / methanol	1:1
B6: dichloromethane / methanol	85:15
B7: dichloromethane / methanol	7:1
B8: dichloromethane / methanol	7:3
B9: dichloromethane / methanol	97:3
B10: dichloromethane	
C1: dichloromethane / methanol / ammonium hydroxide	95: 5:0.5
C2: dichloromethane / methanol / ammonium hydroxide	90:10:1
C3: dichloromethane / methanol / ammonium hydroxide	80:20:2
C4: dichloromethane / methanol / ammonium hydroxide	98:2:0.2
C5: dichloromethane / methanol / ammonium hydroxide	350:50:1
C6: dichloromethane / methanol / ammonium hydroxide	96:4:0.4
C7: dichloromethane / methanol / ammonium hydroxide	70:30:3
C8: dichloromethane / methanol / ammonium hydroxide	60:4:1
C9: dichloromethane / methanol / ammonium hydroxide	20:4:1
C10: dichloromethane / methanol / ammonium hydroxide	40:4:1
D1: dichloromethane / methanol / water / acetic acid	170:26:3:1
D2: dichloromethane / methanol / water / acetic acid	150:54:10:1
E1: ethyl acetate / ethanol / ammonium hydroxide	6:3:1
E2: ethyl acetate / methanol / ammonium hydroxide	40:10:1
F1: toluene / isopropanol / acetic acid	85:15:1
G1: toluene / ethanol / chloroform / ammonium hydroxide	85:15:1

Example 1: 2-Cyclohexylamino-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (1.2 g) and cyclohexylamine (0.69 ml) is heated to for 4 min to produce a melt which is dissolved in isopropanol (15 ml). 4 N HCl in dioxane (0.2 ml) is added and the solvents are removed in vacuo. The residue is

recrystallized from isopropanol and diethylether to give 2-cyclohexylamino-4-phenylamino-quinazoline hydrochloride; m.p. 236 - 238°C, Rf(F1) 0.13.

The starting material can be prepared, for example, as follows:

a) 2-Chloro-4-phenylamino-quinazoline

A solution of 2,4-dichloro-quinazoline (15 g), N,N-diisopropyl-ethylamine (24.9 ml) and aniline (7.5 ml) in isopropanol (75 ml) is heated to reflux for 45 min. The cold reaction mixture is filtered and the filtrate is concentrated in vacuo. The residue is crystallized from diethylether- toluene (1:1) to give 2-chloro-4-phenylamino-quinazoline, m.p. 194 - 196°C.

b) 2,4-Dichloro-quinazoline

N,N-Dimethylaniline (114.0 g) is added slowly to a solution of 1H,3H-quinazolin-2,4-dione (146.0 g) in phosphorousoxychloride (535.4 ml) while this mixture is heated up to 140°C. After completion of the addition reflux is continued for 20 h. The reaction mixture is filtered and concentrated to give a residue which is added to ice and water. The product is extracted with dichloromethane and crystallized from diethylether and petroleum ether to yield 2,4-dichloro-quinazoline, m.p. 115 - 116°C.

Example 2: cis/trans-2-(4-Piperidin-1-yl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.76 g) and N-(4-amino-cyclohexyl)-piperidine (*J. Amer. Chem. Soc.* **1946**, *68*, 1296) (0.6 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (10 ml). 4 N HCl in dioxane (1.0 ml) is added and the solvents are removed in vacuo. The residue is chromatographed on silica gel by eluting with ethyl acetate / methanol / ammonia (8:2:1) to give the free base which, dissolved in ethanol and treated with an excess of 4 N HCl in dioxane, yields cis/trans-2-(4-piperid-1-yl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride, Rf (E1) 0.13.

Example 3: 2-Cyclohexylamino-8-methoxy-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.285 g) and cyclohexylamine (0.15 ml) is heated for 2 min to produce a melt which is dissolved in isopropanol. 4 N HCl in

dioxane (0.1 ml) is added. Crystallization from isopropanol and diethylether yields 2-cyclohexylamino-8-methoxy-4-phenylamino-quinazoline hydrochloride, m.p. 195 - 197°C.

The starting material can be prepared, for example, as follows:

2-Chloro-8-methoxy-4-phenylamino-quinazoline

A solution of 2,4-dichloro-8-methoxy-quinazoline (prepared as described in *J. Chem. Soc.* **1948**, 1759) (0.6 g), diisopropylethylamine (0.87 ml), and aniline (0.26 ml) in isopropanol (10 ml) is heated at reflux for 45 min. The cold reaction mixture is filtered and residue is crystallized from dichloromethane and hexanes to give 2-chloro-8-methoxy-4-phenylamino-quinazoline, m.p. 245 - 246°C.

Example 4: trans-2-(4-Acetoxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride

A solution of trans-2-(4-hydroxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride (1.3 g) and acetic anhydride (0.33 ml) in acetic acid (5 ml) is stirred at ambient temperature for 16 h. The solvent is removed in vacuo and the residue is added to 2N aqueous NaOH. Extraction with ethyl acetate followed by chromatography on silica gel (A4) gives a crude product which is treated with 4 N HCl in dioxane. Crystallization from acetonitrile and acetone yields trans-2-(4-acetoxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 217 - 220°C.

The starting material can be prepared, for example, as follows:

2-(4-Hydroxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (2.3 g) and trans-4-amino-cyclohexanol (1.26 g) is heated for 3 min to produce a melt which is dissolved in isopropanol. 4 N HCl in dioxane (0.1 ml) is added. Crystallization from isopropanol and acetone yields 2-(4-hydroxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 258 - 259°C.

Example 5: trans-Naphthalene-1-sulfonic acid [4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (Example 1a) (0.256 g) and trans-naphthalene-1-sulfonic acid (4-amino-cyclohexylmethyl)-amide (0.364 g) in iso-propanol (5 ml) is stirred at 120 °C for 17 h. After cooling to room temperature, the solvent is removed under reduced pressure. The residue is recrystallized from 1-octanol to give trans-naphthalene-1-sulfonic acid [4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide hydrochloride as colorless crystals melting at 174-176 °C; Rf(B2) 0.32, FAB-MS:  $(M+H)^+ = 537$ .

The starting material can be prepared, for example, as follows:

a) trans-4-[(1-Naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid

To a stirred solution of trans-4-(aminomethyl)-cyclohexanecarboxylic acid (60 g) in 1 N NaOH (917 ml) is added 1-naphthalenesulfonyl chloride (86.59 g) over 30 min at room temperature. The mixture is stirred at room temperature for 20 h. To the mixture is added 140 ml of 4 N HCl and 1 l of water, and the white crystals are collected by filtration to yield trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid as a white powder melting at 164 - 165 °C; Rf(A1) 0.16, FAB-MS:  $(M+H)^+ = 348$ .

b) trans-4-[(1-Naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid amide

To a stirred solution of trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid (100 g) and triethylamine (41.8 ml) in THF (500 ml) is added a solution of ethyl chloroformate (28.6 ml) in THF (30 ml) below 0 °C over 25 min. After stirring at 0 °C for 45 min, 25% aqueous ammonia solution (500 ml) is added to the above mixture at 0 - 5 °C over 10 min. The resulting mixture is stirred at room temperature for 90 min. To the mixture is added 2 l of water and the white solid is collected by filtration to give trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid amide as a white powder melting at 170 - 171 °C; Rf(C5) 0.40, FAB-MS:  $(M+H)^+ = 347$ .

c) trans-Naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide

To a stirred suspension of trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid amide (61.4 g) in THF (500 ml) is added a solution of diborane-THF complex in THF (1 M, 443 ml) below 28 °C over 50 min. The mixture is slowly warmed up and heated up to reflux for 2 h. After cooling to 0 °C, the reaction is quenched by adding 120 ml of water and 500 ml of 4 N HCl. To the mixture is added 1 l of methanol and the mixture is

concentrated under reduced pressure. The residue is treated with 1 l of methanol and concentrated under reduced pressure. The crude product is obtained as its HCl salt and is purified by recrystallization from isopropanol (mp. 259 °C). To the purified HCl salt is added 1.2 l of 1 N NaOH and the resulting solution is extracted with dichloromethane. The combined extracts are dried over sodium sulfate and concentrated under reduced pressure to give trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide as a colorless amorphous solid; Rf(C5) 0.07.

d) trans-Naphthalene-1-sulfonic acid (4-isocyano-cyclohexylmethyl)-amide

To a stirred solution of trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid (3 g) and triethylamine (1.45 ml) in THF (30 ml) is added dropwise to a solution of ethyl chloroformate (0.81 ml) in THF (4 ml) between -10 and -5 °C. After stirring at -10 °C for 20 min, a solution of sodium azide (1.12 g) in water (3.5 ml) is added to the mixture over 5 min. The resulting mixture is stirred for 30 min and is poured into 60 ml of ice-water. The mixture is extracted with toluene. After drying over sodium sulfate, the combined extracts are heated at reflux for 1 h. The solvent is removed under reduced pressure to give trans-naphthalene-1-sulfonic acid (4-isocyano-cyclohexylmethyl)-amide as a colorless oil; Rf(A1) 0.73.

e) trans-Naphthalene-1-sulfonic acid (4-amino-cyclohexylmethyl)-amide

A suspension of trans-naphthalene-1-sulfonic acid (4-isocyano-cyclohexylmethyl)-amide (1.3 g) in 20 ml of 4 N HCl is heated at reflux over night. The white solid is isolated by filtration and is washed with water. To the solid is added 15 ml of 1 N aqueous NaOH and the mixture is extracted with dichloromethane. The combined extracts are dried over sodium sulfate and concentrated under reduced pressure to give trans-naphthalene-1-sulfonic acid (4-amino-cyclohexylmethyl)-amide as a white powder melting at 137 - 138 °C; Rf(C5) 0.1, FAB-MS: (M+H)<sup>+</sup> = 319.

Example 6: trans-Naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-yl-amino)-cyclohexylmethyl]-amide hydrochloride

A suspension of 2-chloro-quinazolin-4-ylamine (see: US 3,956,495) (0.118 g) and trans-naphthalene-1-sulfonic acid (4-amino-cyclohexylmethyl)-amide (0.21 g) in 5 ml of isopentylalcohol is heated up to 120 °C for 15 h. The resulting solution is concentrated and

chromatographed (silica gel, B2) to give the product as a foam. This material is taken up in dichloromethane and treated at 0 °C with a 4 N HCl solution in dioxane (0.2 ml). Concentration in vacuo provides a foam which is triturated in boiling cyclohexane to yield after filtration trans-naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-yl-amino)-cyclohexylmethyl]-amide hydrochloride, melting at 115 - 125 °C. Rf(B2) 0.24; FAB-MS: (M+H)<sup>+</sup> = 462.

Example 7: trans-[4-(4-Phenylamino-quinazoline-2-ylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (9.72 g) and trans-(4-amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester (10.1 g) in isopentylalcohol (150 ml) is stirred at 120 °C for 20 h. The reaction mixture is cooled to ambient temperature and the product is collected by suction filtration. Crystallization from isopropanol yields naphthalene-1-sulfonic acid trans-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide hydrochloride as a colorless crystals melting at 161 - 163 °C; Rf(D1) 0.44.

The starting material can be prepared, for example, as follows:

a) [4-(tert.-Butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester

To a stirred suspension of 4-(tert.-butoxycarbonylaminomethyl)-cyclohexanecarboxylic acid (obtained according to: FR 2,701,480) (45 g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) is added triethylamine (32 ml) below 0 °C over a period of 20 min. The mixture is slowly warmed up and stirred at 70 °C for 4 h. After cooling to 40 °C, benzyl alcohol (36 ml) is added and the reaction mixture is heated at reflux for 20 h. The cold reaction mixture is washed with water and brine and dried over magnesium sulfate. Concentration in vacuo followed by crystallisation from ethyl acetate and diethylether yields [4-(tert.-butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester as colorless crystals, melting at 126 - 129 °C. Rf(A7) 0.47.

b) trans-(4-Amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester

A solution of [4-(tert.-butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester (4 g) in methanol (200 ml) is hydrogenated in the presence of palladium on charcoal 10% (0.7 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate



is concentrated in vacuo to yield and trans-(4-amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester as a colorless oil, Rf(D1) 0.12.

Example 8: trans-4-(Aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride

A suspension of trans-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide hydrochloride (6.8 g) in chloroform (50 ml) is treated with a 4 N HCl solution in dioxane (20 ml) at 0 °C. After completion, the reaction mixture is concentrated in vacuo and the residue is recrystallized from isopropanol to yield trans-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride as white crystals melting at 326 - 330°C. The dihydrochloride salt is taken up in a saturated aqueous potassium carbonate solution and dichloromethane. After extraction with ethyl acetate, the organics are dried over sodium sulfate and concentrated to give trans-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline as a light yellow oil. Rf(G1) 0.04. FAB-MS: (M+H)<sup>+</sup> = 348.

Example 9: trans-[4-(4-Phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-methanesulfonamide hydrochloride

A solution of trans-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline (0.70 g) and diisopropylethylamine (0.41 ml) in dichloromethane (10 ml) or is cooled to 0 °C and treated with methanenesulfonylchloride (0.16 ml) in dichloromethane (2 ml). After completion, the reaction mixture is concentrated and the residue is taken up in water and extracted with ethyl acetate. The combined extracts are washed with brine, dried over magnesium sulfate and concentrated. The residue is dissolved in methanol and treated with a 4 N HCl in dioxane (0.5 ml). Concentration in vacuo followed by crystallization from isopropanol yields trans-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-methanesulfonamide hydrochloride melting at 240-245 °C. Rf(G1) 0.45.

Example 10: trans-4-Methyl-N-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-benzenesulfonamide hydrochloride

Reaction of trans-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline (0.79 g) with toluenesulfonylchloride (0.38 g) as described in Example 9 provides trans-4-methyl-N-

[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-benzenesulfonamide hydrochloride melting at 163-165 °C. Rf(G1) 0.53.

Example 11: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-methoxy-benzenesulfonamide hydrochloride

A solution of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) and diisopropylethylamine (0.716 ml) in 4 ml of N,N-dimethylformamide is cooled to 0 °C and treated with 4-methoxybenzenesulfonylchloride (0.242 g) in N,N-dimethylformamide (2 ml). After completion, the reaction mixture is concentrated and the residue is chromatographed (silica gel, C1) to give the product as a foam. It is taken up in dichloromethane (2 ml) and treated at 0 °C with a 4 N HCl in dioxane (2 ml).

Concentration in vacuo followed by crystallization from acetonitrile yields trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-methoxy-benzenesulfonamide hydrochloride as a tan powder melting at 118 - 125 °C. Rf(C1) 0.38; FAB-MS: (M+H)<sup>+</sup> = 456.

The starting material can be prepared, for example, as follows:

a) trans-(4-Hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

A solution of trans-4-(tert-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (obtained according to: EP 0614 911 A1) (34.5 g) and triethylamine (28 ml) in dichloromethane (700 ml) is cooled to -70 °C and treated with methylchloroformate (12.9 ml). The reaction mixture is stirred 0.5 h at -70 °C. The temperature is allowed to increase to 0 °C and the solution is stirred another 0.5 h until completion of the reaction. The reaction mixture is taken up in ice-cold dichloromethane, washed with an ice-cold 0.5 N HCl solution, a saturated aqueous sodium carbonate solution and water. The organics are dried over sodium sulfate and concentrated to the mixed-anhydride as an oil. This material is taken up in THF and treated at -70 °C with sodium borohydride (5.90 g), followed by absolute methanol (10 ml). The reaction mixture is stirred 15 h at 0 °C and 1 h at ambient temperature to drive the reaction to completion. A 0.5 N HCl solution is then carefully added at 0 °C, followed by ethyl acetate. The organics are washed with a saturated aqueous sodium carbonate solution, water, dried over sodium sulfate and concentrated.

Chromatography on silica gel (A1) yields trans-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as a white powder, melting at 88 - 89°C. Rf(A1) 0.24.

**b) trans-(4-Azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester**

trans-(4-Hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (24 g) in pyridine (200 ml) at 0 °C is treated with a solution of para-toluenesulfonylchloride (24.44 g) in pyridine (50 ml). The reaction mixture is stirred at 0 °C until completion and concentrated in vacuo. The residue is taken up in ethyl acetate, washed with water and dried over sodium sulfate. Concentration of the solution yields the tosylate, used without further purification. This material is treated with sodium azide (19.23 g) in N,N-dimethylformamide (800 ml) at 50°C. After completion of the reaction, the solution is concentrated and the resulting paste is taken up in dichloromethane, washed with water and concentrated. Chromatography of the crude material on silica gel (A2 then A3) provides trans-(4-azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(A3) 0.33; IR (dichloromethane)  $\mu$  max 2099 cm<sup>-1</sup>.

**c) trans-(4-Aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester**

trans-(4-Azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (24 g) in ethyl acetate (1 liter) is hydrogenated over platinumoxide (2.4 g) at ambient temperature under atmospheric pressure of hydrogen. The catalyst is filtered-off and the filtrate concentrated to yield trans-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(C2) 0.41.

**d) trans-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester**

A suspension of 5.0 g of 2-chloro-quinazolin-4-ylamine and 6.75 g of trans-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester in 120 ml of isopentylalcohol is heated up to 120 °C for 15 h. The reaction mixture is concentrated and chromatographed on silica gel (B1 then B2) to give trans-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester as a foam. Rf(B2) 0.33.

**e) trans-N-2-(4-Aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride**

A solution of trans-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (9.58 g) in 130 ml of dichloromethane is cooled to 0 °C and treated with

130 ml of a 4 N HCl solution in dioxane. After completion, the reaction mixture is concentrated in vacuo to yield trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride melting at 189 - 192°C. Rf(C3) 0.54.

Example 12: trans-3-{{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-sulfamoyl}-4-methoxy-benzoic acid methyl ester hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) with 2-methoxy-5-(methoxycarbonyl)-sulfonylchloride (0.332 g) as described in Example 11 provides trans-3-{{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-sulfamoyl}-4-methoxy-benzoic acid methyl ester hydrochloride melting at 140 - 150°C. Rf(C1) 0.28; FAB-MS: (M+H)<sup>+</sup> = 514.

The starting material can be prepared, for example, as follows:

a) 2-Methoxy-5-(methoxycarbonyl)-sulfonic acid

A solution of methyl 4-methoxybenzoate (50 g) in dichloromethane (800 ml) is cooled to 0 °C, treated by slow addition of chlorosulfonic acid (22.10 ml) and heated up to reflux for 12 h. The reaction mixture is cooled to ambient temperature and the product is collected by suction filtration. Crystallization from diethylether yields 2-methoxy-5-(methoxycarbonyl)-sulfonic acid melting at 159 - 160°C.

b) 3-Chlorosulfonyl-4-methoxy-benzoic acid methyl ester

A solution of 2-methoxy-5-(methoxycarbonyl)-sulfonic acid (55 g) in N,N-dimethylformamide (1 liter) is treated at 0 °C with pyridine (53.6 ml), followed by phosphorus oxychloride (61.5 ml) and stirred at ambient temperature for 15 h. The reaction mixture is taken up in diethylether and washed with ice-cold water. The organics are concentrated to ca. 150 ml and the product is allowed to crystallize out overnight. It is collected by suction filtration, triturated in hexanes and dried to give chlorosulfonyl-4-methoxy-benzoic acid methyl ester, melting at 124 - 126 °C.

Example 13: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2,5-dimethoxy-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) with 2,5-dimethoxy-benzenesulfonylchloride (0.258 g) as described in Example 11 provides trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2,5-dimethoxy-benzenesulfonamide hydrochloride melting at 137 - 145°C. Rf(C1) 0.20; FAB-MS: (M+H)<sup>+</sup> = 486.

Example 14: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) with benzenesulfonylchloride (0.161 ml) as described in Example 11 provides trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-benzenesulfonamide hydrochloride melting at 111 - 123 °C. Rf(B2) 0.23; FAB-MS: (M+H)<sup>+</sup> = 426.

Example 15: trans-Naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.2 g) with naphthalene-2-sulfonylchloride (0.127 mg) as described in Example 11 provides trans-naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)methyl]-cyclohexylmethyl}-amide hydrochloride melting at 105 - 120 °C. Rf(C2) 0.63; FAB-MS: (M+H)<sup>+</sup> = 476.

Example 16: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methanesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with methanesulfonylchloride (0.121 ml) as described in Example 11 provides trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methanesulfonamide hydrochloride melting at 130 - 140°C. Rf(C2) 0.35; FAB-MS: (M+H)<sup>+</sup> = 364.

Example 17: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-phenylmethanesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) with phenylmethanesulfonylchloride (0.223 g) as described in Example 11 provides trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-phenylmethanesulfonamide hydrochloride melting at 144 - 150 °C. Rf(C1) 0.32; FAB-MS: (M+H)<sup>+</sup> = 440.

Example 18: trans-N-{4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-tert-butyl-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.26 g) with 4-tert-butyl-benzenesulfonylchloride (0.253 g) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-tert-butyl-benzenesulfonamide hydrochloride melting at 135 - 150°C. Rf(C2) 0.38; FAB-MS: (M+H)<sup>+</sup> = 482.

Example 19: trans-N-{4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2,4,6-trimethyl-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.27 g) with 2,4,6-trimethylbenzenesulfonylchloride (0.24 g) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2,4,6-trimethyl-benzenesulfonamide hydrochloride melting at 148 - 158 °C. Rf(C2) 0.35; FAB-MS: (M+H)<sup>+</sup> = 468.

Example 20: trans-N-{4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-methyl-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.38 g) with para-toluenesulfonylchloride (0.303 g) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-methyl-

benzenesulfonamide hydrochloride melting at 100 - 112 °C. Rf(C2) 0.53; FAB-MS: (M+H)<sup>+</sup> = 440.

Example 21: trans-N-{4-[4-Amino-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-benzamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with benzoylchloride (0.129 ml) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-benzamide hydrochloride melting at 150 - 160 °C. Rf(C2) 0.45; FAB-MS: (M+H)<sup>+</sup> = 390.

Example 22: trans-N-{4-[4-Amino-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-2-phenyl-acetamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with phenylacetylchloride (0.148 ml) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-2-phenyl-acetamide hydrochloride melting at 130 - 138 °C. Rf(C2) 0.55; FAB-MS: (M+H)<sup>+</sup> = 404.

Example 23: trans-N,N-Dimethylamino sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with N,N-dimethylaminosulfonylchloride (0.12 ml) as described in Example 11 provides trans-N,N-Dimethylamino sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 63 - 71 °C. Rf(C1) 0.13; FAB-MS: (M+H)<sup>+</sup> = 393.

Example 24: trans-Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

A suspension of 2-chloro-quinazolin-4-ylamine (7.02 g) and trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (13 g) in 250 ml of isopentylalcohol is heated up to 120 °C for 15 h. The resulting solution is concentrated and chromatographed (silica

gel, B2) to give the product as a foam. This material is taken up in dichloromethane (250 ml) and treated at 0 °C with a 4 N HCl solution in dioxane (10 ml). Concentration in vacuo provides a foam which is triturated in boiling cyclohexane to yield after filtration trans-naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 155 - 164°C. Rf(B2) 0.23; FAB-MS: (M+H)<sup>+</sup> = 476.

The starting material can be prepared, for example, as follows:

a) trans-{4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester

A solution of trans-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (17 g) and ethyldiisopropylamine (14.41 ml) in N,N-dimethylformamide (350 ml) is cooled to 0 °C and treated with a solution of naphthalene-1-sulfonylchloride (15.9 g) in N,N-dimethylformamide (100 ml). The reaction is stirred at ambient temperature for 2 h, concentrated in vacuo. The residue is taken up in dichloromethane, washed with a 0.5 N HCl solution, a saturated aqueous sodium carbonate solution and water, dried and concentrated. Crystallization from hexanes-ethyl acetate gives trans-{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester as a white powder, melting at 199 - 200 °C. Rf(A1) 0.42.

b) trans-Naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide

A suspension of trans-{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (25 g) in chloroform (300 ml) is treated with a 4 N HCl solution in dioxane (300 ml) at 0°C. After completion, the reaction mixture is concentrated in vacuo, the residue is taken up in a 1 N aqueous NaOH solution and dichloromethane. After extraction with dichloromethane, the organics are dried over sodium sulfate and concentrated to 18.5 g of trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide as a white powder melting at 157 - 162 °C. Rf(C3) 0.36.

Example 25: trans-{Naphthalene-1-sulfonic acid 4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

According to the procedure described in Example 24, 0.28 g of 2-chloro-8-methoxy-quinazolin-4-ylamine and 0.444 g of trans-naphthalene-1-sulfonic acid (4-aminomethyl-



cyclohexylmethyl)-amide are reacted together to give trans-naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride, melting at 153 - 160 °C. Rf(B2) 0.21; FAB-MS: (M+H)<sup>+</sup> = 506.

The starting material can be manufactured, for example, as follows:

2-Chloro-8-methoxy-quinazolin-4-ylamine

A solution of 1 g of 2,4-dichloro-8-methoxy-quinazoline in THF (13 ml) is treated with 0.782 ml of ammonium hydroxide (28 % in water). After completion of the reaction (5 h at ambient temperature), the solution is concentrated in vacuo and the residue is recrystallized twice from dioxane to give 2-chloro-8-methoxy-quinazolin-4-ylamine, melting at 146 - 152 °C. Rf(A1) 0.18.

Example 26: trans-Naphthalene-1-sulfonic acid {4-[(4-amino-6-bromo-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

A suspension of 6-bromo-2-chloro-quinazolin-4-ylamine (1.293 g) and trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (1.662 g) in 50 ml of isopentylalcohol is heated up to 120 °C for 15 h. The resulting solution is concentrated and chromatographed (silica gel, ethyl acetate) to give trans-naphthalene-1-sulfonic acid {4-[(4-amino-6-bromo-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide as a foam, melting at 233 - 235°C. Rf(A6) 0.36; FAB-MS: (M+H)<sup>+</sup> = 554.

Example 27: trans-Naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

According to the procedure described in Example 24, 0.28 g of 2-chloro-8-methoxy-quinazolin-4-ylamine and 0.444 g of trans-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide give trans-naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride, melting at 130 - 140 °C. Rf(B4) 0.59; FAB-MS: (M+H)<sup>+</sup> = 506.

The starting material can be prepared, for example, as follows:

a) trans-{4-[(Naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester

According to the procedure described in Example 24a, 5 g of trans-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester and 4.67 g of trans-naphthalene-2-sulfonylchloride give {4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester, melting at 138 - 140 °C. Rf(A4) 0.29.

b) trans-Naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide

According to the procedure described in Example 24b, 5.49 g of trans-{4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester is converted to trans-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide, melting at 123 - 126 °C. Rf(C2) 0.39.

Example 28: trans-Naphthalene-1-sulfonic acid {4-[(4-oxo-3,4-dihydro-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

According to the procedure described in Example 26, 1.36 g of 2-chloro-4 (1H)-quinazolinone and 2.5 g of trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide give trans-naphthalene-1-sulfonic acid {4-[(4-oxo-3,4-dihydro-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide, melting at 225 - 235 °C. Rf(B2) 0.52; FAB-MS: (M+H)<sup>+</sup> = 477.

Example 29: trans-Naphthalene-1-sulfonic acid {4-[(4-phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

According to the procedure described in Example 24, 0.28 g of 2-chloro-4-phenylamino-quinazoline and 0.26 g of trans-naphthalene-1-sulfonic acid -(4-aminomethyl-cyclohexylmethyl)-amide is converted to yield trans-naphthalene-1-sulfonic acid {4-[(4-phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide, melting at 145 - 153 °C. Rf(B1) 0.19; FAB-MS: (M+H)<sup>+</sup> = 552.

Example 30: trans-Naphthalene-1-sulfonic acid {4-[(4-tert-butylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

A mixture of 2-chloro-4-tert.-butyl-amino-quinazoline (0.118 g) and trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.216 g) is heated for 2 min to produce a melt which is dissolved in acetonitrile. 4N HCl in dioxane (0.1 ml) is added and the solvents are removed in vacuo. The residue is dissolved in ethyl acetate and treated with 1N HCl. The aqueous layer is made alkaline with 2 N aqueous NaOH, the product is extracted with ethyl acetate. After concentration in vacuo the residue is redissolved in acetone, 0.1 ml 4N HCl in dioxane is added and crystallization yields trans-naphthalene-1-sulfonic acid {4-[(4-tert.-butylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride, m.p. 238 - 240 °C.

The starting material can be prepared, for example, as follows:

2-Chloro-4-tert.-butylamino-quinazoline

A solution of 2,4-dichloro-quinazoline (2 g) and tert-butylamine (1.46 ml) in isopropanol (5 ml) is heated to 80 °C in a sealed vessel for 30 min. The reaction mixture is concentrated in vacuo and the residue is added to 2 N aqueous NaOH solution and extracted with ethyl acetate. Crystallization from diethylether and hexanes yields 2-chloro-4-tert.-butylamino-quinazoline, m.p. 143 - 145 °C.

Example 31: (R,S)-cis-Naphthalene-1-sulfonic acid {3-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Following the procedure described in Example 24, a mixture of 0.259 g of 2-chloro-quinazolin-4-ylamine and 0.48 g of (R,S)-cis-naphthalene-1-sulfonic acid (3-aminomethyl-cyclohexylmethyl-amide) is converted to (R,S)-cis-naphthalene-1-sulfonic acid 3-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride melting at 152 - 160 °C. Rf(B2) 0.37; FAB-MS: (M+H)<sup>+</sup> = 476.

The starting material can be prepared, for example, as follows:

a) (R,S)-cis-(3-Amino methyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

A solution of 4.0 g of (3-amino methyl-benzyl)-carbamic acid tert-butyl ester in absolute methanol (80 ml) is hydrogenated over Nishimura catalyst (0.8 g) under atmospheric

pressure of hydrogen and at ambient temperature. After completion of the reaction, the catalyst is filtered-off, the filtrate is concentrated and chromatographed on silica gel (C2) to yield (R,S)-cis-(3-amino methyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(C2) 0.33.

**b) (R,S)-cis-{3-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester**

Following the procedure described in Example 24a, a mixture of 1.2 g of (R,S)-cis-(3-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester and 1.12 g of naphthalene-1-sulfonylchloride in acetonitrile are reacted together to yield (R,S)-cis-{3-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester melting at 63 - 68°C. Rf(A4) 0.42.

**c) (R,S)-cis-Naphthalene-1-sulfonic acid (3-aminomethyl-cyclohexylmethyl)-amide**

Following the procedure described in Example 24b, (R,S)-cis-{3-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (1.86 g) is converted to (rac.)-cis-naphthalene-1-sulfonic acid (3-aminomethyl-cyclohexylmethyl)-amide as a foam. Rf(C2) 0.50.

**Example 32: trans-Naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-ylamino)-cyclohexylethyl]-amide hydrochloride**

A solution of 2-chloro-quinazolin-4-ylamine (0.18 g) and trans-naphthalene-1-sulfonic acid (4-aminoethyl-cyclohexylmethyl)-amide (0.345 g) in 6 ml of iso-propanol is stirred at 120 °C for 16h. After cooling to room temperature, the solvent is removed under reduced pressure. The residue is purified by flash column chromatography on silica gel (A2 and B2) to yield trans-naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-ylamino)-cyclohexylethyl]-amide hydrochloride as colorless amorphous solid; Rf(B2) 0.34, FAB-MS: (M+H)<sup>+</sup> = 490.

The starting material can be prepared, for example, as follows:

**a) trans-Naphthalene-1-sulfonic acid [(4-hydroxymethyl)-cyclohexylmethyl]-amide**

To a suspension of lithium aluminum hydride (4.72 g) in THF (100 ml) is added a solution of trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid (28.8 g) in THF

(60 ml) in a dropwise manner below 10 °C. The mixture is stirred at room temperature for 1 h and is heated at reflux for 15 h. The resulting mixture is cooled to 0 °C and a mixture of 100 ml of THF and 15 ml of water is carefully added. To the mixture is added 15 ml of 1 N NaOH and the suspension is stirred for 2 h at room temperature. 40 g of magnesium sulfate and 20 g of Celite are added to the mixture and the inorganic solid is removed by filtration. The filtrate is concentrated under reduced pressure and the residual solid is recrystallized from a mixture of THF and isopropanol to give trans-naphthalene-1-sulfonic acid [(4-hydroxymethyl)-cyclohexylmethyl]-amide as a colorless crystals melting at 134 - 135 °C; Rf(A1) 0.25.

**b) trans-Naphthalene-1-sulfonic acid {[4-(p-toluenesulfonyl-oxy)-methyl]-cyclohexylmethyl}-amide**

To a solution of trans-[(4-hydroxymethyl)-cyclohexylmethyl]-amide (15 g) and triethylamine (12.5 ml) in 200 ml of dichloromethane is added p-toluenesulfonyl chloride (9.86 g) and N,N-dimethylaminopyridine (0.55 g) at room temperature. The mixture is stirred at room temperature for 12 h and is poured into 300 ml of water. The mixture is extracted with dichloromethane. The combined extracts are washed with 0.5 N HCl, aqueous saturated sodium carbonate solution and brine. After drying over sodium sulfate, the solvent is removed under reduced pressure and the residual solid is recrystallized from a mixture of dichloromethane and hexanes to give trans-naphthalene-1-sulfonic acid {[4-(para-toluene sulfonyl)-oxy-methyl]-cyclohexylmethyl}-amide as white crystals melting at 153 - 155 °C; Rf(A1) 0.56.

**c) trans-Naphthalene-1-sulfonic acid [(4-cyanomethyl)-cyclohexylmethyl]-amide**

To a solution of trans-[(4-(p-toluenesulfonyl)-oxy-methyl)-cyclohexylmethyl]-amide (10.8 g) in N,N-dimethylformamide (100 ml) is added sodium cyanide (4.34 g) at room temperature. The mixture is stirred at 50 °C for 20 h. After cooling to room temperature, N,N-dimethylformamide is removed under reduced pressure. The residue is suspended in water and is extracted with ethyl acetate. The combined extracts are washed with water and brine and are dried over sodium sulfate. The solvent is removed under reduced pressure and the residual solid is recrystallized from a mixture of dichloromethane and hexanes to give trans-naphthalene-1-sulfonic acid [(4-cyanomethyl)-cyclohexylmethyl]-amide as colorless crystals melting at 136 - 138 °C; Rf(A1) 0.50, FAB-MS: (M+H)<sup>+</sup> = 343.

d) trans-Naphthalene-1-sulfonic acid [(4-aminoethyl)-cyclohexylmethyl]-amide

A suspension of naphthalene-1-sulfonic acid trans-[(4-cyanomethyl)-cyclohexylmethyl]-amide (2.0 g) and Raney nickel (0.5 g) in methanol (50 ml) containing 5% ammonia is stirred under hydrogen at room temperature for 16 h. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure. To the residue is added 4 N HCl in dioxane (10 ml) at 0 °C and the resulting solution is stirred for 30 min. The mixture is concentrated under reduced pressure and the residual solid is washed with diethylether. To the solid is added 1 N NaOH (25 ml) solution and the mixture is extracted with dichloromethane. The combined extracts are dried over sodium sulfate and are concentrated under reduced pressure to give naphthalene-1-sulfonic acid trans-[(4-aminoethyl)-cyclohexylmethyl]-amide as white amorphous solid; Rf(B3) 0.46, FAB-MS:  $(M+H)^+ = 347$ .

Example 33: In a manner analogous to that described herein before it is also possible to manufacture the following compounds:

Naphthalene-1-sulfonic acid {4-[[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[[4-(2-hydroxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[[4-[2-(2-hydroxyethyl)-ethylamino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[[4-[2-(morpholin-1-yl)-ethylamino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[[4-[1,1-di(hydroxymethyl)-methylamino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[[4-(3-methoxy-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[[4-(4-methylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[[4-(N,N-dimethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-yl)-methyl-amino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methyl-amide.

*cis*-Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-(acetylamino)-benzenesulfonamide.

N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethyl-benzenesulfonamide.

N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-nitro-benzenesulfonamide.

Quinoline-8-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-fluoro-benzenesulfonamide.

Cyclohexane-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Propane-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

2-Methoxyethane sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Morpholine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Piperidine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

4-Methyl-piperazine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N,N-Dimethylaminosulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N-Methylaminosulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxyethoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-8-(N,N-dimethylaminoethoxy)-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-8-(morpholin-4-ylethoxy)-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-8-ethyl-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-6-methoxyethoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-5,8-dimethoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Piperidine-1-sulfonic acid {3-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-2-sulfonic acid {3-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N-{3-[(4-Amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-(N,N-dimethylamino)-sulfonamide.

Naphthalene-2-sulfonic acid {3-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclopentylmethyl}-amide.

8-Methoxy-2-{4-(naphthalen-ylmethanesulfonylmethyl)-cyclohexylmethyl}-quinazoline-2,4-diamine.

4-(Chloro-phenylamino)-8-methoxy-2-(4-pyrrolidin-1-ylmethyl-cyclohexylamino)-quinazoline

4-(Chloro-phenyl)-8-methoxy-2-methyl-2-(4-pyrrolidin-1-ylmethyl-cyclohexyl)-quinazoline-2,4-diamine

1-{4-[4-(4-Chloro-phenyl)-8-methoxy-quinazolin-2-ylamino]-cyclohexylmethyl}-pyrrolidin-2-one

{4-[4-(4-Chloro-phenyl)-6-dimethylamino-quinazolin-2-ylamino]-cyclohexylmethyl}-N-methyl-acetamide

2-{4-(4-Chloro-phenylamino)-2-[4-(propane-2-sulfonylmethyl)-cyclohexylamino]-quinazolin-8-yloxy}-ethanol

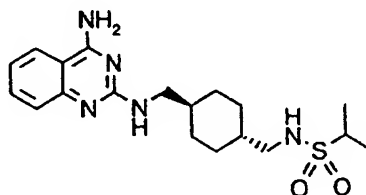
2-[6-Chloro-4-(4-chloro-phenylamino)-2-[4-(propane-2-sulfonylmethyl)-cyclohexylamino]-quinazolin-8-yloxy]-ethanol

6-Chloro-4-(4-Chloro-phenyl)-8-(2-methoxy-ethoxy)-2-[4-[2-(propane-2-sulfonyl)-ethyl]-cyclohexyl]-quinazoline-2,4-diamine



2-{4-[8-(2-Dimethylamino-ethoxy)-4-(4-fluoro-phenylamino)-quinazolin-2-ylamino]-cyclohexyl}-ethanesulfonic acid dimethylamide  
 N,N-Dimethylsulfonic acid 4-[4-(4-chloro-phenylamino)-8-methoxy-quinazolin-2-ylamino]-cyclohexylmethyl]-amide  
 3-{4-[4-(4-Chloro-phenylamino)-8-(2-hydroxy-ethoxy)-quinazolin-2-ylamino]-cyclohexyl}-1-(4-methyl-piperazin-1-yl)-propan-1-one

Example 34: trans-Propane-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride



A solution of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.5 g) and diisopropylethylamine (1.19 ml) in 6 ml of N,N-dimethylformamide is cooled to 0 °C and treated with isopropyl-sulfonylchloride (1.09 ml) in N,N-dimethylformamide (1 ml). After completion, the reaction mixture is concentrated and the residue is chromatographed (silica gel, C1) to give the product as a foam. It is taken up in dichloromethane (2 ml) and treated at 0 °C with a 4 N HCl in dioxane (2 ml). Concentration in vacuo followed by crystallization from acetonitrile yields *trans*-propane-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride as a powder melting at 120-130 °C. R<sub>f</sub>(C1) 0.21; FAB-MS: (M+H)<sup>+</sup> = 392.

The starting material can be prepared, for example, as follows:

a) trans-(4-Hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

A solution of *trans*-4-(tert-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (EP 0614 911 A1) (34.5 g) and triethylamine (28 ml) in dichloromethane (700 ml) is cooled to -70 °C and treated with methylchloroformate (12.9 ml). The reaction mixture is stirred 0.5 h at -70 °C. The temperature is allowed to increase to 0 °C and the solution is stirred another 0.5 h until completion of the reaction. The reaction mixture is taken up in ice-cold dichloromethane, washed with an ice-cold 0.5 N HCl solution, a saturated aqueous sodium

carbonate solution and water. The organics are dried over sodium sulfate and concentrated to 41.3 g of mixt-anhydride as an oil. This material is taken up in THF and treated at - 70 °C with sodium borohydride (5.90 g), followed by absolute methanol (10 ml). The reaction mixture is stirred 15 h at 0 °C and 1 h at ambient temperature to drive the reaction to completion. A 0.5 N HCl solution is then carefully added at 0 °C, followed by ethyl acetate. The organics are washed with a saturated aqueous sodium carbonate solution, water, dried over sodium sulfate and concentrated. Chromatography on silica gel (A1) yields *trans*-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as a white powder, melting at 88 - 89 °C. Rf(A1) 0.24.

b) *trans*-(4-Azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

*trans*-(4-Hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (24 g) in pyridine (200 ml) at 0 °C is treated with a solution of para-toluenesulfonylchloride (24.44 g) in pyridine (50 ml). The mixture is stirred at 0 °C until completion of the reaction and concentrated in vacuo. The residue is taken up in ethyl acetate, washed with water and dried over sodium sulfate. Concentration of the solution yields the tosylate, used without further purification. This material is treated with sodium azide (19.23 g) in N,N-dimethylformamide (800 ml) at 50 °C. After completion of the reaction, the solution is concentrated and the resulting paste is taken up in dichloromethane, washed with water and concentrated. Chromatography of the crude material on silica gel (A2 then A3) gives *trans*-(4-azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(A3) 0.33; IR (dichloromethane)  $\nu$  max 2099 cm<sup>-1</sup>.

c) *trans*-(4-Aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

*trans*-(4-Azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (24 g) in ethyl acetate (1 liter) is hydrogenated over platinumoxide (2.4 g) at ambient temperature under atmospheric pressure of hydrogen. The catalyst is filtered off and the filtrate concentrated to yield *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(C2) 0.41.

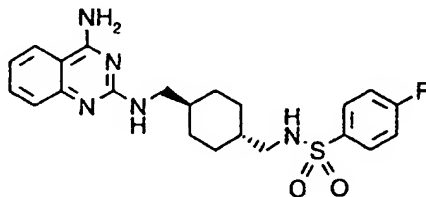
d) *trans*-(4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl)-carbamic acid tert-butyl ester

A suspension of 5.0 g of 2-chloro-quinazolin-4-ylamine and 6.75 g of *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester in isopentylalcohol (120 ml) is heated up to 120 °C for 15 h. The reaction mixture is concentrated and chromatographed on silica gel (B1 then B2) to give *trans*-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester as a foam. Rf(B2) 0.33.

e) *trans*-N(2)-(4-Aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride

A solution of *trans*-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (9.58 g) in dichloromethane (130 ml) is cooled to 0 °C and treated with a 4N HCl solution in dioxane (130 ml). After completion, the reaction mixture is concentrated in vacuo to yield *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride melting at 189 - 192 °C. Rf(C3) 0.54.

Example 35: *trans*-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-fluoro-benzenesulfonamide hydrochloride

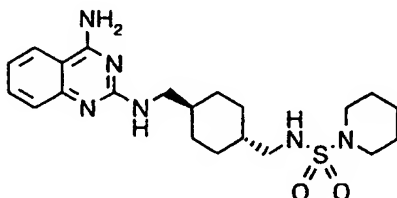


Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with 4-fluorobenzenesulfonylchloride (0.326 g) as described in Example 34 gives *trans*-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-fluoro-benzenesulfonamide hydrochloride as a powder melting at 95-102 °C. Rf(B2) 0.30; FAB-MS: (M+H)<sup>+</sup> = 444.

Example 36: *trans*-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-nitro-benzenesulfonamide hydrochloride

Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.5 g) with 2-nitrobenzenesulfonylchloride (0.433 g) as described in 34 gives *trans*-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-nitro-benzenesulfonamide hydrochloride as a powder melting at 129-138 °C. Rf(C1) 0.15; FAB-MS: (M+H)<sup>+</sup> = 471.

Example 37: trans-Piperidine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride



Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with 0.246 g of piperidinesulfonylchloride (WO 94/05639) as described in Example 34 gives *trans*-piperidine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride as a powder melting at 92-95 °C. Rf(C3) 0.70; FAB-MS: (M+H)<sup>+</sup> = 433.

Example 38: trans-Morpholine-4-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with 0.311 g of 4-morpholinesulfonylchloride (WO 94/05639) as described in Example 34 gives *trans*-morpholine-4-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride as a powder melting at 125 °C. Rf(C2) 0.41; FAB-MS: (M+H)<sup>+</sup> = 435.

Example 39: trans-Naphthalene-1-sulfonic acid {4-[(4-(2-methoxy-ethylamino)-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

A suspension of (2-chloro-quinazolin-4-yl)-(2-methoxy-ethyl)-amine ((0.37 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.518 g) in isopentylalcohol (10 ml) is heated to 120 °C for 18 h. The reaction mixture is concentrated and the residue is chromatographed (silica gel, B1) to give *trans*-naphthalene-1-sulfonic acid {4-[(4-(2-methoxy-ethylamino)-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide as a powder melting at 105-110 °C. Rf(B2) 0.33; FAB-MS: (M+H)<sup>+</sup> = 534.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-(2-methoxy-ethyl)-amine

A solution of 2,4-dichloro-quinazoline (5 g) and diisopropylethylamine (8.6 ml) in isopropanol (30 ml) is treated with 2-methoxyethylamine (2.07 g) in isopropanol (10 ml). Under completion of the reaction (exothermic), the crude mixture is concentrated and the residue partitioned between water and dichloromethane. The aqueous phase is extracted with dichloromethane, the organics are combined and dried over magnesium sulfate.

Chromatography (silica gel, A4 followed by A1) gives (2-chloro-quinazolin-4-yl)-(2-methoxy-ethyl)-amine as a powder melting at 122-125 °C. Rf(A1) 0.52.

Example 40: *trans*-Naphthalene-2-sulfonic acid {4-[[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-(2-methoxy-ethyl)-amine (0.37 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.518 g) (see Example 27b for preparation) according to Example 40, followed by chromatography (silica gel, B1) gives *trans*-naphthalene-2-sulfonic acid {4-[[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a foam melting at 101-106 °C. Rf(B2) 0.36; FAB-MS: (M+H)<sup>+</sup> = 534.

Example 41: *trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-hydroxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of 2-(2-chloro-quinazolin-4-ylamino)-ethanol (0.3 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.446 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-hydroxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a foam melting at 107-110 °C. Rf(C1) 0.05; FAB-MS: (M+H)<sup>+</sup> = 520.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-ylamino)-ethanol

The reaction of 2,4-dichloro-quinazoline (5 g) and ethanolamine (1.68 g) according to Example 40a, followed by crystallization from dichloromethane gives 2-(2-chloro-quinazolin-4-ylamino)-ethanol as a white powder melting at 173-177 °C. Rf(A8) 0.26.

Example 42: trans-Naphthalene-1-sulfonic acid {4-[[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of 2-(2-chloro-quinazolin-4-ylamino)-propane-1,3-diol (0.4 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.524 g) according to Example 40, followed by chromatography (silica gel, C2) and crystallization from acetonitrile gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a white powder melting at 186-188 °C. Rf(C2) 0.24; FAB-MS: (M+H)<sup>+</sup> = 550.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-ylamino)-propane-1,3-diol

The reaction of 2,4-dichloro-quinazoline (9 g) and 2-amino-1,3-propane-diol (4.12 g) in methanol according to the procedure described in Example 40a, followed by crystallization from methanol gives 2-(2-chloro-quinazolin-4-ylamino)-propane-1,3-diol as a white powder melting at 185-186 °C. Rf(A6) 0.17.

Example 43: trans-Naphthalene-1-sulfonic acid {4-[[4-(3-methoxy-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of 2-(2-chloro-quinazolin-4-yl)-(3-methoxy-propyl)-amine (0.35 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.462 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(3-methoxy-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 82-85 °C. Rf(C1) 0.20; FAB-MS: (M+H)<sup>+</sup> = 548.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-yl)-(3-methoxy-propyl)-amine

The reaction of 2,4-dichloro-quinazoline (9 g) and 3-methoxy-propylamine (4.03 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, A4) gives 2-(2-chloro-quinazolin-4-yl)-(3-methoxy-propyl)-amine as a white powder melting at 89-90 °C. Rf(A4) 0.20.

Example 44: trans-Naphthalene-1-sulfonic acid {4-[[4-[2-(2-hydroxy-ethoxy)-ethylamino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of 2-[2-(2-chloro-quinazolin-4-ylamino)-ethoxy]-ethanol (0.4 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.497 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-[2-(2-hydroxy-ethoxy)-ethylamino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 90-92 °C. Rf(C1) 0.09; FAB-MS: (M+H)<sup>+</sup> = 564.

The starting material can be prepared, for example, as follows:

2-[2-(2-Chloro-quinazolin-4-ylamino)-ethoxy]-ethanol

The reaction of 2,4-dichloro-quinazoline (9 g) and 2-(2-aminoethoxy)-ethanol (4.75 g) according to the procedure described in Example 40a, followed by crystallization from diethylether gives 2-[2-(2-chloro-quinazolin-4-ylamino)-ethoxy]-ethanol as a white powder melting at 108-109 °C. Rf(A8) 0.12.

Example 45: trans-Naphthalene-1-sulfonic acid {4-[[4-methylamino-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-methyl-amine (0.3 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.515 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-methylamino-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a tan foam melting at 100-110 °C. Rf(C1) 0.16; FAB-MS: (M+H)<sup>+</sup> = 490.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-methyl-amine

2,4-Dichloro-quinazoline (22 g) in THF (330 ml) is treated with a 40% aqueous solution of methylamine (24.85 ml). Upon completion of the reaction (exothermic) the crude mixture is concentrated *in vacuo* and the residue triturated in dioxane. Crystallization from water gives (2-chloro-quinazolin-4-yl)-methyl-amine as a white powder melting at 212-214 °C. Rf(A1) 0.41.

Example 46: trans-Naphthalene-1-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-dimethyl-amine (0.3 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.48 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide as a powder melting at 87-94 °C. Rf(C1) 0.32; FAB-MS: (M+H)<sup>+</sup> = 504.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-dimethyl-amine

2,4-Dichloro-quinazoline (7 g) in THF (100 ml) is treated with a 40% aqueous solution of dimethylamine (11.57 ml). Upon completion of the reaction (exothermic), concentration *in vacuo*, followed by aqueous work-up and chromatography (silica gel, dichloromethane) (2-chloro-quinazolin-4-yl)-dimethyl-amine is obtained as a powder melting at 112-114 °C. Rf(dichloromethane) 0.12.

Example 47: trans-Naphthalene-1-sulfonic acid {4-[(4-morpholin-4-yl-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

The reaction of 2-chloro-4-morpholin-4-yl-quinazoline (0.4 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.533 g) according to Example 40, followed by chromatography (silica gel, C4) gives *trans*-naphthalene-1-sulfonic acid {4-[(4-morpholin-4-yl-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide as a powder melting at 95-100 °C. Rf(C6) 0.24; FAB-MS: (M+H)<sup>+</sup> = 546.

The starting material can be prepared, for example, as follows:

2-Chloro-4-morpholin-4-yl-quinazoline

The reaction of 2,4-dichloro-quinazoline (9 g) and morpholine (3.93 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, A4) gives 2-chloro-4-morpholin-4-yl-quinazoline as a white powder melting at 112-113 °C. Rf(A4) 0.30.



Example 48: trans-Naphthalene-1-sulfonic acid {4-[[4-(4-methyl-piperazin-1-yl)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

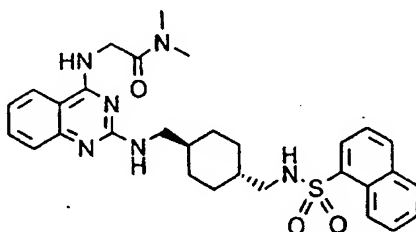
The reaction of 2-chloro-4-(4-methyl-piperazin-1-yl)-quinazoline (1 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (1.39 g) according to Example 40, followed by chromatography (silica gel, B4) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(4-methyl-piperazin-1-yl)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 103-107 °C. Rf(B4) 0.46; ESI-MS: (M+H)<sup>+</sup> = 559.

The starting material can be prepared, for example, as follows:

2-Chloro-(4-methoxy-piperidin-1-yl)-quinazoline

The reaction of 2,4-dichloro-quinazoline (10 g) and 1-methylpiperazine (6.14 ml) according to the procedure described in Example 40a, followed by chromatography (silica gel, B2) gives 2-chloro-4-(4-methyl-piperazin-1-yl)-quinazoline as a powder melting at 83-84 °C. Rf(B2) 0.54.

Example 49: trans-N,N-Dimethyl-2-{2-[[4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl]-amino]-quinazolin-4-ylamino}-acetamide



The reaction of 2-(2-chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide (1.5 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (2.07 g) according to Example 40, followed by chromatography (silica gel, B4) gives *trans*-N,N-dimethyl-2-{2-[[4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl]-amino]-quinazolin-4-ylamino}-acetamide as a powder melting at 132-143 °C. Rf(C1) 0.35; ESI-MS: (M+H)<sup>+</sup> = 561.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide

The reaction of 2,4-dichloro-quinazoline (10 g) and 2-amino-N,N-dimethyl-acetamide (5.64 g) according to the procedure described in Example 40a, followed by trituration in boiling hexanes gives 2-(2-chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide as a powder melting at 190-192 °C. Rf(A1) 0.10.

Example 50: trans-N,N-Dimethyl-2-{2-[[4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl]-amino]-quinazolin-4-ylamino}-acetamide

The reaction of 2-(2-chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide (1 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (1.38 g) according to Example 40, followed by chromatography (silica gel, B4) gives *trans*-N,N-dimethyl-2-{2-[[4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl]-amino]-quinazolin-4-ylamino}-acetamide as a powder melting at 124-131 °C. Rf(B4) 0.56; ESI-MS: (M+H)<sup>+</sup> = 561.

Example 51: trans-Naphthalene-1-sulfonic acid {4-[[4-(2-piperidin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine (0.6 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.857 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-piperidin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 116-120 °C. Rf(C1) 0.20; ESI-MS: (M+H)<sup>+</sup> = 587.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide

The reaction of 2,4-dichloro-quinazoline (9 g) and 2-piperidino-ethylamine (5.79 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, B2) gives (2-chloro-quinazolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine as a powder melting at 117-120 °C. Rf(B2) 0.26.

Example 52: trans-Naphthalene-1-sulfonic acid {4-[[4-(2-morpholin-4-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-(2-morpholin-4-yl-ethyl)-amine (0.7 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.994 g) according to

Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-morpholin-4-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 114-119 °C. Rf(C1) 0.18; ESI-MS: (M+H)<sup>+</sup> = 589.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-(2-morpholin-4-yl-ethyl)-amine

The reaction of 2,4-dichloro-quinazoline (9 g) and 4-(2-aminoethyl)-morpholine (5.88 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, C1) gives (2-chloro-quinazolin-4-yl)-(2-morpholin-4-yl-ethyl)-amine as a powder melting at 106-108 °C. Rf(C1) 0.31.

Example 53: *trans*-Naphthalene-1-sulfonic acid {4-[[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide hydrochloride

The reaction of N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-propane-1,3-diamine (1.5 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (2.35 g) according to Example 40, followed by chromatography (silica gel, C2) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide hydrochloride as a powder melting at 130-140 °C. Rf(C2) 0.22; ESI-MS: (M+H)<sup>+</sup> = 561.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-quinazolin-4-yl)-N',N'-dimethyl-propane-1,3-diamine

The reaction of 2,4-dichloro-quinazoline (10 g) and 3-dimethylamino-1-propylamine (5.13 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, B4 then B5) gives N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-propane-1,3-diamine as a powder melting at 64-72 °C. Rf(B2) 0.10.

Example 54: *trans*-Naphthalene-2-sulfonic acid {4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

A solution of N-(2-fluoro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (0.4 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.682 g) in isopentylalcohol (50 ml) was heated to 80 °C for 4 h, then concentrated *in vacuo*. Aqueous

work-up followed by chromatography (silica gel, C1) gives *trans*-naphthalene-2-sulfonic acid {4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 96 °C. Rf(C2) 0.32; ESI-MS: (M+H)<sup>+</sup> = 547. Analysis for C<sub>30</sub>H<sub>38</sub>N<sub>6</sub>O<sub>2</sub>S+0.5H<sub>2</sub>O: C 64.8%; H 7.1%; N 15.1%; S 5.8%; O 7.2%, found: C 64.2%; H 6.9%; N 14.9%; S 5.6%; O 6.8%.

The starting material can be prepared, for example, as follows:

N-(2-Fluoro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine

A solution of 2,4-difluoro-quinazoline (0.85 g) (prepared from 2,4-dichloro-quinazoline according to: Schroeder, H. *et al. J. Org. Chem.* 1962, 27, 2580) in N,N-dimethylformamide (25 ml) is treated with a solution of 2-dimethylaminoethylamine (0.84 ml) of in N,N-dimethylformamide (5 ml) at 0 °C. After completion of the reaction (0.25 h at 0 °C), the reaction mixture is concentrated *in vacuo* and the residue is chromatographed (silica gel, B2) to give N-(2-fluoro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine as a powder melting at 103-106 °C. Rf(B2) 0.22.

Example 55: *trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

Reaction of N-(2-fluoro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (1.26 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (2.14 g) according to Example 54 followed by chromatography (silica gel, C1) and crystallization from isopropylether gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 112-115 °C. Rf(C2) 0.40; ESI-MS: (M+H)<sup>+</sup> = 547. Analysis for C<sub>30</sub>H<sub>38</sub>N<sub>6</sub>O<sub>2</sub>S+0.5H<sub>2</sub>O: C 64.8%; H 7.1%; N 15.1%; S 5.8%; O 7.2%, found: C 63.3%; H 7.0%; N 15.2%; S 5.5%; O 8.6%.

Example 56: *trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-diethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

A mixture of N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride (3 g), *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (3.48 g), diisopropylethylamine (4.9 ml) and phenol (13.4 g) is heated to 150 °C for 3 h to produce a

melt. The reaction mixture is taken up in dichloromethane, washed with a 1N aqueous sodium hydroxide solution, brine and dried over sodium sulfate. Concentration *in vacuo* followed by crystallization from isopropylether/isopropanol gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-diethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 160-162 °C. Rf(C2) 0.38; ESI-MS: (M+H)<sup>+</sup> = 575.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride

A suspension of 2,4-dichloro-quinazoline (30 g) in isopropanol (200 ml) is treated by dropwise addition of a solution of N,N-diethylethylenediamine (23.3 ml) in isopropanol (50 ml) in an exothermic reaction. The reaction mixture is cooled to 0 °C, the voluminous precipitate is collected by suction filtration and dried *in vacuo* to give N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride as a powder melting at 205-206 °C. Rf(B2) 0.20.

Example 57: *trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-dimethylamino-1,1-dimethyl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

Reaction of N(2)-(2-chloro-quinazolin-4-yl)-2,N(1),N(1)-trimethyl-propane-1,2-diamine (0.6 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.716 g) according to Example 56 followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-dimethylamino-1,1-dimethyl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 89-93 °C. Rf(C1) 0.28; ESI-MS: (M+H)<sup>+</sup> = 575.

The starting material can be prepared, for example, as follows:

N(2)-(2-Chloro-quinazolin-4-yl)-2,N(1),N(1)-trimethyl-propane-1,2-diamine

The reaction of 2,4-dichloro-quinazoline (9.07 g) and 2-dimethylamino-1,1-dimethyl-ethylamine (5.3 g) (prepared from 1-dimethylamino-2-methyl-2-nitropropane, see: Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 12 and Freifelder, M. *et al. J. Org. Chem.* **1965**, *30*, 4370) according to the procedure described in Example 56a, followed by an aqueous sodium bicarbonate wash and chromatography (silica gel, B1) gives N(2)-(2-chloro-

quinazolin-4-yl)-2,N(1),N(1)-trimethyl-propane-1,2-diamine as a powder melting at 92-95 °C. Rf(B1) 0.36.

Example 58: trans-Naphthalene-1-sulfonic acid {4-{{4-[2-(4-methyl-piperazin-1-yl)-ethylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-[2-(4-methyl-piperazin-1-yl)-ethyl]-amine (0.8 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (1.08 g) according to Example 40, followed by chromatography (silica gel, E2) gives *trans*-naphthalene-1-sulfonic acid {4-{{4-[2-(4-methyl-piperazin-1-yl)-ethylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide as a powder melting at 107-110 °C. Rf(E2) 0.64; ESI-MS: (M+H)<sup>+</sup> = 602.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-[2-(4-methyl-piperazin-1-yl)-ethyl]-amine

The reaction of 2,4-dichloro-quinazoline (7 g) and 2-(4-methyl-piperazin-1-yl)-ethylamine (5.03 g) (*Bull. Soc. Chim. France* 1962, 556) according to the procedure described in Example 40a, followed by chromatography (silica gel, B2) gives (2-chloro-quinazolin-4-yl)-[2-(4-methyl-piperazin-1-yl)-ethyl]-amine as a powder melting at 58-60 °C. Rf(B2) 0.15.

Example 59: trans-Naphthalene-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

Reaction of N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride (2 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (2.22 g) according to Example 56 followed by crystallization from isopropylether/isopropanol gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 135-136 °C. Rf(C2) 0.19; ESI-MS: (M+H)<sup>+</sup> = 589.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride

The reaction of 2,4-dichloro-quinazoline (30 g) and N,N-diethyl-1,3-diamino-propane (26.1 ml) according to the procedure described in Example 56a, followed by crystallization from

isopropylether/isopropanol gives N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine as a powder melting at 163-164 °C. Rf(C2) 0.32.

Example 60: trans-Propane-2-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

A solution of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine (0.3 g) and diisopropylethylamine (0.39 ml) in N,N-dimethylformamide is treated with a solution of isopropylsulfonylchloride (0.125 ml) in acetonitrile. Upon completion of the reaction, the solution is concentrated *in vacuo* and the residue is chromatographed (silica gel, C2) to give *trans*-propane-2-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a yellow powder melting at 50-53 °C. Rf(C2) 0.27; ESI-MS: (M+H)<sup>+</sup> = 505.

The starting material can be prepared, for example, as follows:

trans-N(2)-(4-Aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine

A mixture of N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine (3 g) and *trans*-1,4-cyclohexane-bis-(methylamine) (6.48 g) (Lancaster, >98% *trans*) as a paste is heated up for 3 minutes to produce a melt. Chromatography (silica gel, C3) gives *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine as a glass. Rf(C3) 0.15; ESI-MS: (M+H)<sup>+</sup> = 399.

Example 61: trans-4-Methyl-piperazine-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine (0.3 g) and 4-methyl-piperazin-1-ylsulfonylchloride hydrochloride (0.212 g) (WO92/13545) as described in Example 60 followed by chromatography (silica gel, C2) gives *trans*-4-methyl-piperazine-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a yellow powder melting at 75-77 °C. Rf(C2) 0.29; ESI-MS: (M+H)<sup>+</sup> = 561.

Example 62: trans-N-{4-[[4-(3-Diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-C-phenylmethanesulfonamide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine (0.3 g) and phenylmethanesulfonylchloride (0.172 g) as described in Example 60 followed by chromatography (silica gel, C2) gives *trans*-N-{4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-C-phenylmethanesulfonamide as a white powder melting at 62-63 °C. Rf(C2) 0.23; ESI-MS: (M+H)<sup>+</sup> = 553.

Example 63: trans-Naphthalene-2-sulfonic acid {4-[[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine (0.4 g) and naphthalene-2-sulfonylchloride (0.367 g) as described in Example 60 followed by chromatography (silica gel, C2) gives *trans*-naphthalene-2-sulfonic acid {4-[[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 83-86 °C. Rf(C2) 0.34; ESI-MS: (M+H)<sup>+</sup> = 561.

The starting material can be prepared, for example, as follows:

trans-N(2)-(4-Aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine

Reaction of N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-propane-1,3-diamine (2.5 g) and *trans*-1,4-cyclohexane-bis-(methylamine) (5.9 g) according to Example 60a followed by chromatography (silica gel, C3) gives *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine as a foam. Rf(C3) 0.24.

Example 64: trans-N-{4-[[4-(3-Dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-4-fluoro-benzenesulfonamide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine (0.4 g) and 4-fluoro-benzenesulfonylchloride (0.315 g) as described in Example 60 followed by chromatography (silica gel, C2) gives *trans*-N-{4-[[4-(3-

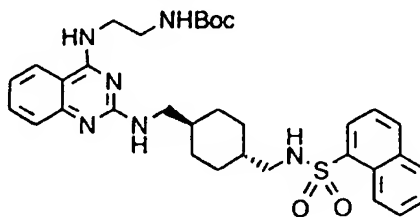


dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl]-4-fluoro-benzenesulfonamide as a powder melting at 74-79 °C. Rf(C2) 0.30; ESI-MS: (M+H)<sup>+</sup> = 529.

Example 65: *trans*-N(4)-(3-Dimethylamino-propyl)-N(2)-{4-[(2-methoxy-benzylamino)-methyl]-cyclohexylmethyl}-quinazoline-2,4-diamine

Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine (0.5 g) and 2-methoxy-benzylbromide (0.462 g) (Kelly, J. L. *et al J. Med. Chem.* 1989, 32, 1757) in N,N-dimethylformamide (11 ml) in the presence of diisopropylethylamine (0.693 ml) at ambient temperature followed by chromatography (silica gel, C3) gives *trans*-N(4)-(3-dimethylamino-propyl)-N(2)-{4-[(2-methoxy-benzylamino)-methyl]-cyclohexylmethyl}-quinazoline-2,4-diamine as a foam melting at 134-140 °C. Rf(C3) 0.28; ESI-MS: (M+H)<sup>+</sup> = 491.

Example 66: *trans*-{2-{2-{4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}quinazolin-4-ylamino)-ethyl}-carbamic acid *tert*-butyl ester



An homogeneous mixture of [2-(2-chloro-quinazolin-4-ylamino)-ethyl]-carbamic acid *tert*-butyl ester (0.5 g) and of *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl-methyl)-amide (0.463 g) is stirred at 200 °C. Upon completion of the reaction the product is chromatographed (silica gel, B2) to give *trans*-{2-{2-{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}quinazolin-4-ylamino)-ethyl}-carbamic acid *tert*-butyl ester as a powder melting at 123-127 °C. Rf(B2) 0.32; ESI-MS: (M+H)<sup>+</sup> = 619.

The starting material can be prepared, for example, as follows:

[2-(2-Chloro-quinazolin-4-ylamino)-ethyl]-carbamic acid *tert*-butyl ester

The reaction of 2,4-dichloro-quinazoline (3.72 g) and N-BOC-ethylenediamine (3 g) according to the procedure described in Example 56a, followed by chromatography (silica

gel, A1) gives [2-(2-chloro-quinazolin-4-ylamino)-ethyl]-carbamic acid *tert*-butyl ester as a white foam. Rf(A1) 0.36.

Example 67: *trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-amino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

A solution of *trans*-{2-[2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}quinazolin-4-ylamino)-ethyl]-carbamic acid *tert*-butyl ester (0.52 g) in dichloromethane (20 ml) is cooled to 0 °C and treated by slow addition of trifluoroacetic acid (20 ml). Upon completion of the reaction, the solution is concentrated *in vacuo* and the residue is chromatographed (silica gel, C3) to give *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-amino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a foam melting at 125-130 °C. Rf(C3) 0.54; ESI-MS: (M+H)<sup>+</sup> = 519.

Example 68: *trans*-4-{2-[2-{{4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino)-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester

The reaction of 4-[2-(2-chloro-quinazolin-4-ylamino)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester (0.45 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl)-cyclohexylmethyl)-amide (0.349 g) according to the procedure described in Example 66, followed by chromatography (silica gel, B2) gives *trans*-4-{2-[2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino)-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester as a foam melting at 115-120 °C. Rf(B2) 0.29; ESI-MS: (M+H)<sup>+</sup> = 689.

The starting material can be prepared, for example, as follows:

4-[2-(2-Chloro-quinazolin-4-ylamino)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester

The reaction of 2,4-dichloro-quinazoline (1.73 g) and 4-(2-amino-ethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (2 g) (prepared from 1-(2-aminoethyl)-piperazine according to: Prugh, J. D. *et al Synth. Comm.* **1992**, 22, 2357) according to the procedure described in Example 56a, followed by chromatography (silica gel, B1) gives 4-[2-(2-chloro-quinazolin-4-ylamino)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester as a foam. Rf(B1) 0.19.

Example 69: trans-Naphthalene-1-sulfonic acid {4-[[4-(2-piperazin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

Treatment of *trans*-4-{2-[2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino]-quinazolin-4-ylamino}-ethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (0.396 g) with trifluoroacetic acid according to Example 67 followed by chromatography (silica gel, C3) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-piperazin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide melting at 135-139 °C. Rf(C3) 0.50; ESI-MS: (M+H)<sup>+</sup> = 588.

Example 70: trans-Naphthalene-1-sulfonic acid {4-[[4-[(2-dimethylamino-ethyl)-methyl-amino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(2-dimethylamino-ethyl)-N(4)-methyl-quinazoline-2,4-diamine (0.3 g) and naphthalene-1-sulfonylchloride (0.275 g) as described in Example 60 followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[[4-[(2-dimethylamino-ethyl)-methyl-amino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide as a powder melting at 70-72 °C. Rf(C1) 0.15; ESI-MS: (M+H)<sup>+</sup> = 561.

The starting material can be prepared, for example, as follows:

a) N-(2-Chloro-quinazolin-4-yl)-N,N',N'-trimethyl-ethane-1,3-diamine hydrochloride

The reaction of 2,4-dichloro-quinazoline (15 g) and N,N,N'-trimethylethylenediamine (7.7 g) according to the procedure described in Example 56a, followed by crystallization from isopropanol gives N-(2-chloro-quinazolin-4-yl)-N,N',N'-trimethyl-ethane-1,3-diamine hydrochloride as a white powder melting at 163-165 °C. Rf(B2) 0.60.

b) trans-N(2)-(4-Aminomethyl-cyclohexylmethyl)-N(4)-(2-dimethylamino-ethyl)-N(4)-methyl-quinazoline-2,4-diamine

Reaction of N-(2-chloro-quinazolin-4-yl)-N,N',N'-trimethyl-ethane-1,3-diamine hydrochloride (1.4 g) and *trans*-1,4-cyclohexane-bis-(methylamine) (3.3 g) according to Example 60a followed by chromatography (silica gel, C2) gives *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(2-dimethylamino-ethyl)-N(4)-methyl-quinazoline-2,4-diamine as an oil. Rf(C2) 0.06.

Example 71: trans-Naphthalene-1-sulfonic acid {4-[[4-amino-quinazolin-2-yl]-methyl-amino]-methyl}-cyclohexylmethyl)-amide hydrochloride

Reaction of 2-chloro-quinazolin-4-yl-amine (0.267 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (0.515 g) according to Example 56 gives *trans*-naphthalene-1-sulfonic acid {4-[[4-amino-quinazolin-2-yl]-methyl-amino]-methyl}-cyclohexylmethyl)-amide hydrochloride melting at 175-180 °C. Rf(C1) 0.62; ESI-MS: (M+H)<sup>+</sup> = 490.

The starting material can be prepared, for example, as follows:

a) trans-4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl chloride

A suspension of *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarboxylic acid (45 g) (prepared as described in Example 38a) in toluene (550 ml) is treated with oxalylchloride (33.4 ml) and 2 drops of N,N-dimethylformamide. The mixture is stirred at 70 °C for 2 h and the resulting solution is concentrated *in vacuo*. The residue is stirred in toluene (200 ml) and cooled to 0 °C. The solids are collected by suction filtration and dried *in vacuo* at 50 °C to give *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl chloride as a white powder melting at 140-142 °C.

b) trans-4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarboxylic acid methylamide

A mixture of *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl chloride (42.5 g) and potassium carbonate (17.66 g) in dichloromethane (1.2 l) and water (120 ml) is cooled to 5 °C and treated with 11 ml of a methylamine solution (40% in water). Upon completion (30 min at 5 °C) the reaction mixture is partitioned between water and dichloromethane. The organics are concentrated *in vacuo* to give *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarboxylic acid methylamide as a white powder melting at 176-177 °C.

c) trans-Naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide

Reaction of *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarboxylic acid methylamide (0.83 g) with borane-THF complex according to Example 5c gives *trans*-

naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide as a white powder melting at 141-142 °C. Rf(C2) 0.14.

Example 72: trans-Naphthalene-1-sulfonic acid {4-[(4-amino-6-fluoro-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide

Reaction of 2-chloro-6-fluoro-quinazolin-4-yl-amine (0.26 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (0.437 g) according to Example 26 gives *trans*-naphthalene-1-sulfonic acid {4-[(4-amino-6-fluoro-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide melting at 118-122 °C. Rf(C1) 0.22; ESI-MS: (M+H)<sup>+</sup> = 494.

The starting material can be prepared, for example, as follows:

2-Chloro-6-fluoro-quinazolin-4-yl-amine

Reaction of 2,4-dichloro-6-fluoro-quinazoline (3 g) (WO 95/32205) and ammonium hydroxide according to Example 25a gives 2-chloro-6-fluoro-quinazolin-4-yl-amine melting at 165-167 °C. Rf(A5) 0.13.

Example 73: trans-Naphthalene-1-sulfonic acid {4-[(4-amino-6-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of 2-chloro-6-methoxy-quinazolin-4-yl-amine (0.5 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (0.793 g) according to Example 24 gives *trans*-naphthalene-1-sulfonic acid {4-[(4-amino-6-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 210-212 °C. Rf(C1) 0.11; ESI-MS: (M+H)<sup>+</sup> = 506.

The starting material can be prepared, for example, as follows:

2-Chloro-6-methoxy-quinazolin-4-yl-amine

Reaction of 2,4-dichloro-6-methoxy-quinazoline (1.3 g) and ammonium hydroxide according to Example 25a gives 2-chloro-6-methoxy-quinazolin-4-yl-amine melting at 167-171 °C. Rf(A1) 0.24.

Example 74: *trans*-Naphthalene-1-sulfonic acid {4-[(4-amino-5-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of 2-chloro-5-methoxy-quinazolin-4-yl-amine (0.25 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (0.397 g) according to Example 24 gives *trans*-naphthalene-1-sulfonic acid {4-[(4-amino-5-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 238-241 °C. Rf(C1) 0.11; ESI-MS: (M+H)<sup>+</sup> = 506.

The starting material can be prepared, for example, as follows:

2-Chloro-5-methoxy-quinazolin-4-yl-amine

Reaction of 2,4-dichloro-5-methoxy-quinazoline (0.8 g) and ammonium hydroxide according to Example 25a gives 2-chloro-5-methoxy-quinazolin-4-yl-amine melting at 220-230 °C. Rf(A1) 0.24.

Example 75: *trans*-Naphthalene-1-sulfonic acid {4-[(4-(2-dimethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

Reaction of N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (1 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (1.42 g) according to Example 56 followed by chromatography (silica gel, C2) and crystallization from isopropylether/isopropanol gives *trans*-naphthalene-1-sulfonic acid {4-[(4-(2-dimethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide melting at 112-115 °C. Rf(C2) 0.36; ESI-MS: (M+H)<sup>+</sup> = 578.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-8-methoxy-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine

Reaction of 2,4-dichloro-8-methoxy-quinazoline (10 g) and 2-dimethylaminoethylamine (4.76 ml) according to Example 40a gives N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine melting at 176-178 °C. Rf(B2) 0.24.

Example 76: *trans*-Naphthalene-1-sulfonic acid {4-[(4-(2-diethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

Reaction of N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride (2g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (2.12 g) according to Example 56 gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(2-diethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide melting at 109-114 °C. Rf(C2) 0.44; ESI-MS: (M+H)<sup>+</sup> = 605.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride

Reaction of 2,4-dichloro-8-methoxy-quinazoline (25 g) and 2-diethylaminoethylamine(18.9 ml) according to Example 56a gives N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride melting at 189-190 °C. Rf(C2) 0.53.

Example 77: *trans*-Naphthalene-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-8-methoxy-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide hydrochloride

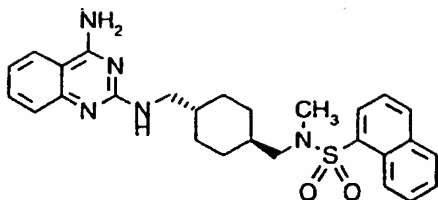
Reaction of N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride (2 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (2.03 g) according to Example 56 followed by chromatography (silica gel, C2), treatment with a 4N HCl solution in dioxane and trituration of the crude material in isopropylether gives *trans*-naphthalene-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-8-methoxy-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 155 °C. Rf(C2) 0.30; ESI-MS: (M+H)<sup>+</sup> = 619.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride

Reaction of 2,4-dichloro-8-methoxy-quinazoline (25 g) and 3-diethylaminopropylamine (18.9 ml) according to Example 56a gives N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride melting at 166-172 °C. Rf(C2) 0.28.

Example 78: *trans*-Naphthalene-1-sulfonic acid {4-[4-amino-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-methyl-amide hydrochloride



A solution of 4-amino-2-chloroquinazoline (0.259 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-methyl-amide (0.5 g) in isopentanol (7.5 ml) is stirred at 120 °C for 19 h. After cooling to room temperature, the solvent is removed under reduced pressure. The residue is purified by flash chromatography to give *trans*-naphthalene-1-sulfonic acid {4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl)-methyl-amide hydrochloride as a colorless amorphous solid: Rf(B2) 0.32; FAB-MS: (M+H)<sup>+</sup> = 490.

The starting material can be prepared, for example, as follows:

a) *trans*-Naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-amide

To a suspension of lithium aluminum hydride (4.72 g) in THF (100 ml) is added under an inert atmosphere of nitrogen a solution of *trans*-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid (28.8 g) in THF (60 ml) below 10 °C. The mixture is stirred at room temperature for 1 h and is then refluxed for 15 h. After cooling to 0 °C, a mixture of THF (100 ml) and water (10 ml) is added followed by aqueous 1N NaOH solution (15 ml) and the resulting suspension is stirred at room temperature for 2 h. After the addition of magnesium sulfate (40 g) and Celite (20 g) the inorganic salts are removed by filtration. The filtrate is concentrated and the crude product is purified by recrystallization from THF-isopropyl ether to give *trans*-naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-amide as white crystals, melting at 134-145 °C: Rf(A1) 0.25.

b) *trans*-Naphthalene-1-sulfonic acid [4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide

To a stirred suspension of *trans*-naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-amide (10 g) in dichloromethane (80 ml) is added 3,4-dihydro-2H-pyran (2.85 ml) and *p*-toluene sulfonic acid monohydrate (57 mg) at room temperature. After stirring at room temperature for 30 min, potassium carbonate (5 g) is added and the resulting suspension is stirred for 5 min. The reaction mixture is diluted with dichloromethane (150 ml), washed with water and brine, dried over sodium sulfate and



concentrated *in vacuo*. The crude product is purified by recrystallization from ether-hexane to obtain *trans*-naphthalene-1-sulfonic acid [4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide as white crystals melting at 126-127 °C: Rf (A1) 0.64.

c) *trans*-Naphthalene-1-sulfonic acid methyl-[4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide

To a stirred solution of *trans*-naphthalene-1-sulfonic acid [4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide (11.0 g) in DMF (60 ml) is added sodium hydride (1.26 g, ca 60 %) at room temperature over a period of 5 min. After stirring at room temperature for 40 min, methyl iodide (1.97 ml) is added in a dropwise manner over 10 min. The reaction mixture is stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue is partitioned between water and ethyl acetate and extracted with ethyl acetate. The combined extracts are washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. Recrystallization from ether-hexane gives *trans*-naphthalene-1-sulfonic acid methyl-[4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide as colorless crystals melting at 91-91 °C: Rf(A3) 0.29.

d) *trans*-Naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-methyl-amide

To a stirred suspension of *trans*-naphthalene-1-sulfonic acid methyl-[4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide (10.0 g) in a mixture of methanol (80 ml) and THF (40 ml) is added p-toluene sulfonic acid monohydrate (0.13 g) at room temperature. After stirring at room temperature for 26 h, potassium carbonate (5 g) is added and the resulting mixture is stirred for 10 min. The inorganic salts are filtered off and the filtrate is concentrated *in vacuo*. The residue is dissolved in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Recrystallization from THF-hexane yields *trans*-naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-methyl-amide as colorless crystals melting at 124-125 °C: Rf(A1) 0.28.

e) *trans*-Toluene-4-sulfonic acid 4-[(methyl-(naphthalene-1-sulfonyl)-amino)-methyl]-cyclohexylmethyl ester

To a stirred solution of *trans*-naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylethyl)-methyl-amide (7.6 g) in dichloromethane (100 ml) is added triethyl amine (5.63 ml). To the

mixture is added p-toluene sulfonyl chloride (4.8 g) and 4-diethylamino-pyridine (0.27 g) at room temperature. The resulting mixture is stirred at room temperature for 6 h and then, is poured into water. The mixture is extracted with dichloromethane. The extract is washed with 1N HCl and aqueous saturated sodium hydrogen carbonate solution and brine. After drying over sodium sulfate, the solvent is removed under reduced pressure to give *trans*-toluene-4-sulfonic acid 4-[[methyl-(naphthalene-1-sulfonyl)-amino]-methyl]-cyclohexylmethyl ester as an oil: Rf (A1) 0.57.

f) *trans*-Naphthalene-1-sulfonic acid (4-azide-methyl-cyclohexylmethyl)-methyl-amide

To a solution of *trans*-toluene-4-sulfonic acid 4-[[methyl-(naphthalene-1-sulfonyl)-amino]-methyl]-cyclohexylmethyl ester (10.9 g) in DMF (100 ml) is added sodium azide (4.94 g) at room temperature. The mixture is stirred at 60°C for 15 h. After cooling to room temperature, DMF is removed under reduced pressure. To the residue is added 150 ml of water and the mixture is extracted with ethyl acetate. The extract is washed with brine and is dried over sodium sulfate. The solvent is removed under reduced pressure. The residue is purified by flash column chromatography on silica gel (hexane-ethyl acetate = 4/1) to give *trans*-naphthalene-1-sulfonic acid (4-azide-methyl-cyclohexylmethyl)-methyl-amide as an oil: Rf (A3) 0.33; FAB-MS (M+H)<sup>+</sup> = 373.

g) *trans*-Naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-methyl-amide

To a solution of *trans*-naphthalene-1-sulfonic acid (4-azide-methyl-cyclohexylmethyl)-methyl-amide (2.5 g) in ethyl acetate (75 ml) is added platinum(IV)-oxide (0.25 g) and the mixture is stirred under an atmosphere of hydrogen at room temperature for 35 min. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure. The crude product is purified by recrystallization from ether-hexane to give *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-methyl-amide as colorless crystals melting at 84-86 °C: Rf(B4) 0.16.

Example 79: *trans*-Naphthalene-1-sulfonic acid methyl-{4-[4-phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

According to the procedure described in Example 78, 2-chloro-4-phenylamino-quinazoline (0.369 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-methyl-amide (0.5 g) are reacted together to give *trans*-naphthalene-1-sulfonic acid methyl-{4-[4-

phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-amide hydrochloride as a colorless amorphous solid: Rf(B2) 0.36; FAB-MS: (M+H)<sup>+</sup> = 566

Example 80: trans-Naphthalene-1-sulfonic acid {4-[1-(4-amino-quinazolin-2-ylamino)-1-methyl-ethyl]cyclohexylmethyl]-amide hydrochloride

A solution of 4-amino-2-chloroquinazoline (0.249g) and *trans*-naphthalene-1-sulfonic acid [4-(1-amino-methyl-ethyl)-cyclohexylmethyl]-amide (0.5 g) in iso-pentanol (7.5 ml) is stirred at 120.°C for 11 days. After removal of the solvent the residue is purified by flash chromatography to give *trans*-naphthalene-1-sulfonic acid {4-[1-(4-amino-quinazolin-2-ylamino)-1-methyl-ethyl]cyclohexylmethyl]-amide hydrochloride as an amorphous solid: Rf(B2) 0.21; FAB-MS: (M+H)<sup>+</sup> = 504.

The starting material can be prepared, for example, as follows:

a) trans-Naphthalene-1-sulfonic acid (4-cyano-cyclohexylmethyl)-amide

To a stirred suspension of *trans*-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid amide (20 g) in toluene (225 ml) is added thionyl chloride (6.28 ml) at room temperature and the reaction mixture is stirred at 80°C for 8 h. The reaction mixture is poured into ice-water (300 ml) and the solution is made alkaline with 4N aqueous NaOH (50 ml) before it is extracted with ethyl acetate. The combined extracts are washed with 1% aqueous sodium carbonate solution and water, dried over sodium sulfate, and concentrated *in vacuo*. The residue is purified by recrystallization from isopropanol to give *trans*-naphthalene-1-sulfonic acid (4-cyano-cyclohexylmethyl)-amide as colorless crystals, melting at 146-148 °C: Rf(A1) 0.56.

b) trans-Naphthalene-1-sulfonic acid [4-(1-amino-methyl-ethyl)-cyclohexylmethyl]-amide

To a stirred suspension of anhydrous cesium trichloride (14.99 g) in THF (125 ml) is added a solution of methyl lithium - lithium bromide complex in diethyl ether (40 ml) below -65 °C. After stirring at -78 °C for 30 min, a solution of *trans*-naphthalene-1-sulfonic acid (4-cyano-cyclohexylmethyl)-amide (5 g) in THF is added to the mixture in a dropwise manner. The mixture is stirred at -78 °C for 5 h and at -40 °C for 16 h. Upon completion, the reaction mixture is quenched with 28% aqueous ammonia (30 ml) and the mixture is allowed to warm to room temperature and is then filtered through Celite. The filtrate is washed with

water, dried over sodium sulfate, and concentrated under reduced pressure. The residue is purified by flash chromatography to give *trans*-naphthalene-1-sulfonic acid [4-(1-amino-methyl-ethyl)-cyclohexylmethyl]-amide as a powder: FAB-MS: (M+H)<sup>+</sup> = 361.

Example 81: *trans*-Naphthalene-1-sulfonic acid {4-[1-methyl-1-(4-phenylamino-quinazolin-2-ylamino)-ethyl]-cyclohexylmethyl}-amide hydrochloride

According to the procedure described in Example 80, 2-chloro-4-phenylamino-quinazoline (0.33 g) and *trans*-naphthalene-1-sulfonic acid [4-(1-amino-methyl-ethyl)-cyclohexylmethyl]-amide (0.465 g) are reacted together to give *trans*-naphthalene-1-sulfonic acid {4-[1-methyl-1-(4-phenylamino-quinazolin-2-ylamino)-ethyl]-cyclohexylmethyl}-amide hydrochloride as an amorphous solid: R<sub>f</sub> (B2) 0.35; FAB-MS: (M+H)<sup>+</sup> = 580.

Example 82: *trans* Naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide hydrochloride

A suspension of 4-amino-2-chloro-quinazoline (0.359 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.637 g) in isopentyl alcohol (4 ml) is stirred at 120 °C for 21 h. The cooled reaction mixture is concentrated *in vacuo* to give a solid which is triturated with dioxane, filtered and then dried overnight under high vacuum to give *trans* naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide hydrochloride as an amorphous solid melting at 209-212 °C. R<sub>f</sub>(C5) 0.47; ESI-MS: (M+H)<sup>+</sup> = 462.

The starting material can be prepared, for example, as follows:

a) *trans*-[4-(Naphthalene-2-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester

A solution of naphthalene-2-sulfonyl chloride (5.12 g) in N,N-dimethylformamide (30 ml) is added dropwise to a milky solution of *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (5.08 g) (Example 58b) and ethyldiisopropylamine (4.7 ml) in N,N-dimethylformamide (100 ml) at 0°C. The reaction is stirred at room temperature for 5.5 h and then concentrated *in vacuo*. The residue is taken up in dichloromethane and washed with 0.5N aqueous HCl, saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate and concentrated. Chromatography on silica gel (B1) yields *trans*-[4-

(naphthalene-2-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester as a tan foam. Rf(B1) 0.40; ESI-MS: (M-H)<sup>-</sup>=417.

b) *trans*-Naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide

A solution of 4N HCl in dioxane (50 ml) is added dropwise over 20 min to a yellow solution of *trans*-[4-(naphthalene-2-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (8.43 g) in dichloromethane (50 ml) at 0 °C. Methanol (10 ml) and additional 4N HCl in dioxane (35 ml) are added after 6 h. The reaction mixture is worked up after 21 h by concentrating *in vacuo*. The residue is taken up in 1N aqueous NaOH and extracted with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated to give an oil. Dilution with hexanes followed by cooling (-20 °C) overnight and then filtration gives *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide as a solid. Rf(C2) 0.11; ESI-MS: (M+H)<sup>+</sup>=319.

In analogous manner as described hereinbefore following compound can be prepared:

Example 83: *trans* Naphthalene-2-sulfonic acid (4-[[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-methyl]-cyclohexyl)-amide hydrochloride

Rf(C5) 0.57; ESI-MS: (M+H)<sup>+</sup>=572, 574.

Example 84: *trans* Naphthalene-1-sulfonic acid (4-[[4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl)-amide

A suspension of 4-amino-2-chloro-quinazoline (0.359 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.637 g) isopentanol (4 ml) is stirred at 120 °C for 21 h. The cooled reaction mixture is concentrated *in vacuo* to give an oily residue. Chromatography on silica gel (B7) gives *trans* naphthalene-1-sulfonic acid (4-[[4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl)-amide as a solid. Rf(C5) 0.43; ESI-MS: (M+H)<sup>+</sup>=462.

The starting material can be prepared, for example, as follows:

a) *trans*-[4-(Naphthalene-1-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester

A solution of naphthalene-1-sulfonyl chloride (5.18 g) in N,N-dimethylformamide (30 ml) is added dropwise to a milky solution of *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (5.05 g) and ethyldiisopropylamine (4.7 ml) in N,N-dimethylformamide (100 ml) at 0°C. The reaction is stirred at room temperature for 5 h and then concentrated *in vacuo*. The residue is taken up in dichloromethane and washed with 0.5N aqueous HCl, saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate and concentrated. The residue is diluted with ethyl acetate, filtered and washed with hexanes to give *trans*-[4-(naphthalene-1-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester as a white powder. Rf(B1) 0.39; ESI-MS: (M-H)=417.

b) *trans*-Naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl)-amide

A solution of 4N HCl in dioxane (50 ml) is added dropwise over 20 min to a yellow solution of *trans*-[4-(naphthalene-1-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (7.90 g) in dichloromethane (45 ml) at 0 °C. Methanol (10 ml) and additional 4N HCl in dioxane (35 ml) are added after 6 h. The reaction mixture is worked up after 21 h by concentrating *in vacuo*. The residue is taken up in 1N aqueous NaOH and extracted with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated to give an oil. Dilution with hexanes followed by cooling (-20 °C) overnight and then filtration gives *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl)-amide as a solid. Rf(C2) 0.08; ESI-MS: (M+H)<sup>+</sup>=319.

Example 85: *trans*-Naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide

A suspension of 4-amino-2-chloro-8-methoxy-quinazoline (0.419 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.637 g) in isopentanol (4 ml) is stirred at 120 °C for 47 h. The cooled reaction mixture is concentrated *in vacuo* to give an oily residue. Dichloromethane and 1N aqueous NaOH are added, and the mixture is stirred at room temperature for 19 h. The suspension is filtered and the phases separated. The aqueous phase is re-extracted with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated. The residue is chromatographed on silica gel (B6-B8) to give *trans* naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexyl}-amide as a beige solid melting at 202-205 °C. Rf(C5) 0.32; ESI-MS: (M+H)<sup>+</sup>=492.

In analogous manner as described hereinbefore following compound can be prepared:

Example 86: trans-Naphthalene-1-sulfonic acid (4-[[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-methyl]-cyclohexyl)-amide

Rf(C5) 0.52; ESI-MS: (M+H)<sup>+</sup>=572, 574.

Example 87: trans-Naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide hydrochloride

A suspension of 4-amino-2-chloro-8-methoxy-quinazoline (0.419 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.637 g) in isopentyl alcohol (4 ml) is stirred at 120 °C for 47 h. The cooled reaction mixture is concentrated *in vacuo* to give a solid which is triturated with dioxane. The suspension is filtered, the filtrate re-concentrated and the resulting residue chromatographed on silica gel (B2-B8) to give *trans* naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide hydrochloride as a light yellow solid. Rf(C5) 0.28; ESI-MS: (M+H)<sup>+</sup>=492.

Example 88: trans Naphthalene-2-sulfonic acid (4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexyl)-amide

A suspension of N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (0.574 g), *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.764 g), ethyldiisopropylamine (1.02 ml) and phenol (2.82 g) is stirred at 150°C for 8 h. The cooled reaction mixture is diluted with dichloromethane and 1N aqueous NaOH and the phases separated. The aqueous phase is re-extracted with dichloromethane and the combined organic layers are washed with brine, dried over sodium sulfate and concentrated. Chromatography on silica gel (B6-B8) gives *trans* naphthalene-2-sulfonic acid (4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexyl)-amide as a light yellow foam. Rf(C5) 0.28; ESI-MS: (M+H)<sup>+</sup>=533.

In analogous manner as described hereinbefore following compound can be prepared:

Example 89: trans Naphthalene-1-sulfonic acid (4-[(4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino)-methyl]-cyclohexyl)-amide

Rf(C5) 0.14; ESI-MS: (M+H)<sup>+</sup>=533.

Example 90: trans-N-{4-[(4-Phenylamino-quinazolin-2-ylamino)]-cyclohexylmethyl}-(N,N-dimethylamino)-sulfonamide hydrochloride

A solution of *trans*-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride (0.35 g) and diisopropylethylamine (0.7 ml) in dichloromethane (10 ml) is cooled to 0 °C and treated with dimethylsulfamoyl chloride (0.3 ml). After stirring at room temperature for 20 h, the reaction mixture is concentrated and the residue is triturated with aqueous sodium hydrogen carbonate, filtered and the dried residue is chromatographed (silica gel, B1) to give the product as an oil. It is taken up in methanol and treated at 0 °C with 4N HCl in dioxane. Concentration in vacuo followed by crystallization from isopropanol and diethyl ether yields *trans*-N-{4-[(4-phenylamino-quinazolin-2-ylamino)]-cyclohexylmethyl}-(N,N-dimethylamino)-sulfonamide hydrochloride as white crystals melting at 230-234 °C. Rf(D1) 0.37; FAB-MS: (M+H)<sup>+</sup>= 455.

The starting material can be prepared, for example, as follows:

a) trans-[4-(tert.-Butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester

To a stirred suspension of *trans*-4-(tert.-butoxycarbonylaminomethyl)-cyclohexanecarboxylic acid (obtained according to: FR 2,701,480) (45 g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) is added triethylamine (32 ml) below 0 °C over a period of 20 min. The mixture is slowly warmed up and stirred at 70 °C for 4 h. After cooling to 40 °C, benzyl alcohol (36 ml) is added and the reaction mixture is heated at reflux for 20 h. The cold reaction mixture is washed with water and brine and dried over magnesium sulfate. Concentration in vacuo followed by crystallization from ethyl acetate and diethyl ether yields *trans*-[4-(tert.-butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester as colorless crystals, melting at 126 - 129 °C. Rf(A7) 0.47.

b) trans-(4-Amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester



A solution of [4-(tert.-butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester (4 g) in methanol (200 ml) is hydrogenated in the presence of palladium on charcoal 10% (0.7 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated in vacuo to yield and *trans*-(4-amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester as a colorless oil, Rf(D1) 0.12.

c) *trans*-[4-(4-Phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (9.72 g) and *trans*-(4-amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester (10.1 g) in isopentylalcohol (150 ml) is stirred at 120 °C for 20 h. The reaction mixture is cooled to ambient temperature and the product is collected by suction filtration. Crystallization from isopropanol yields *trans*-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester hydrochloride as a colorless crystals melting at 161 - 163 °C; Rf(D1) 0.44.

d) *trans*-4-(Aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride

A suspension of *trans*-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester hydrochloride (6.8 g) in chloroform (50 ml) is treated with a 4 N HCl solution in dioxane (20 ml) at 0 °C. After completion, the reaction mixture is concentrated in vacuo and the residue is recrystallized from isopropanol to yield *trans*-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride as white crystals melting at 326 - 330 °C. The dihydrochloride salt is taken up in a saturated aqueous potassium carbonate solution and dichloromethane. After extraction with ethyl acetate, the combined phases are dried over sodium sulfate and concentrated to give *trans*-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline as a light yellow oil. Rf(G1) 0.04. FAB-MS: (M+H)<sup>+</sup> = 348.

Example 91: *trans*-N-(4-{[4-(4-Chloro-phenyl)amino]-quinazolin-2-ylamino}-cyclohexylmethyl)-(N,N-dimethylamino)-sulfonamide hydrochloride

According to the procedure described in Example 90, *trans*-4-(aminomethyl-cyclohexylamino)-4-(4-chloro-phenyl)amino-quinazoline dihydrochloride (0.36 g), diisopropylethylamine (0.6 ml) and dimethylsulfamoyl chloride (0.2 ml) are reacted together to give *trans*-N-(4-{[4-(4-chloro-phenyl)amino]-quinazolin-2-ylamino}-cyclohexylmethyl)-(N,N-di-

methylamino)-sulfonamide hydrochloride as a white powder melting at 206-212 °C: Rf(H1) 0.44, ESI-MS: (M+H)<sup>+</sup>=489.

In analogous manner as described hereinbefore following compound can be prepared:

Example 92: trans-N-(4-{[4-(4-Fluoro-phenyl)amino]-8-methoxy-quinazolin-2-ylamino}-cyclohexylmethyl)-(N,N-dimethylamino)-sulfonamide hydrochloride

167-169 °C: Rf(H1) 0.46, FAB-MS: (M+H)<sup>+</sup>=503.

Example 93: trans-N-{4-[4-(Cyclopropylmethylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-methanesulfonamide hydrochloride

258-262 °C. Rf(D1) 0.35.

Example 94: trans-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester

According to the procedure described in Example 78, 2-chloro-4-(4-chloro-phenyl)-amino-quinazoline (8.7 g), diisopropylethylamine (6 ml) and *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (8.4 g) are reacted together to give *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester as white crystals melting at 235-238 °C. Rf(H1) 0.42.

In analogous manner as described hereinbefore following compound can be prepared:

Example 95: trans-{4-[4-(Cyclopropylamino)-8-methoxy-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester

224-227 °C. Rf(H1) 0.46.

Example 96: trans-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-acetamide hydrochloride

A solution of *trans*-(4-aminomethyl-cyclohexyl)-4-(4-chloro-phenyl)-quinazoline-2,4-diamine dihydrochloride (0.955 g) and diisopropylethylamine (1 ml) in 25 ml of dichloromethane is cooled to 0 °C and treated with acetic anhydride (0.28 ml). After stirring for 1 h at room temperature, the reaction mixture is diluted with aqueous potassium carbonate and extracted with dichloromethane. The combined extracts are dried and concentrated *in vacuo*. The residue is taken up in methanol and treated at 0 °C with a 4 N HCl in dioxane. Concentration *in vacuo* followed by crystallization from ethanol and acetonitrile yields *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-acetamide hydrochloride as white crystals melting at 300-304 °C. Rf(H1) 0.32.

The starting material can be prepared, for example, as follows:

*trans*-4-(Aminomethyl-cyclohexyl)-4-(4-chloro-phenyl-quinazolin-2,4-diamine dihydrochloride

According to the procedure described in Example 90b *trans*-{4-[4-(4-chloro-phenylamino)-quinazoline-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester hydrochloride (2.44 g) and 5N HCl solution in isopropanol (20 ml) are reacted together to give *trans*-(4-aminomethyl-cyclohexyl)-4-(4-chloro-phenylamino)-quinazoline-2,4-diamine dihydrochloride as an amorphous solid: Rf(H1) 0.14, ESI-MS: (M+H)<sup>+</sup> = 382, 384.

Example 97: *trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-benzamide hydrochloride

According to the procedure described in Example 94 *trans*-(4-aminomethyl-cyclohexyl)-4-(4-chloro-phenylamino)-quinazoline-2,4-diamine dihydrochloride (0.32 g), diisopropylethylamine (0.26 g) and benzoic anhydride (0.26 g) are reacted together to give *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-benzamide hydrochloride as white crystals melting at 245-248 °C. Rf(H1) 0.23, ESI-MS: (M+H)<sup>+</sup> = 486, 488.

Example 98: *trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-2-methoxy-benzamide hydrochloride

According to the procedure described in Example 78, 2-chloro-4-(4-chloro-phenyl)-amino-quinazoline (0.725 g), diisopropylethylamine (0.51 ml) and *trans*-(4-amino-cyclohexylmethyl)-2-methoxy-benzamide (0.656 g) are reacted together to give *trans*-{4-[4-(4-

chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl)-2-methoxy-benzamide hydrochloride as light yellow crystals melting at 242-245 °C: Rf(H1) 0.43, ESI-MS: (M+H)<sup>+</sup> = 516, 418.

The starting material can be prepared, for example, as follows:

a) trans-(-Aminomethyl-cyclohexyl)-carbamic acid benzylester hydrochloride

According to the procedure described in Example 90b, *trans*-[4-(*tert*-butoxycarbonyl-aminomethyl)-cyclohexyl]-carbamic acid benzylester (49 g) and 4N HCl solution in dioxane (20 ml) are reacted together to give *trans*-(-aminomethyl-cyclohexyl)-carbamic acid benzylester hydrochloride as white crystals melting at 194-197 °C: Rf(G1) 0.10.

b) {4-[(2-Methoxy-benzoylamino)-methyl]-cyclohexyl}-carbamic acid benzylester

According to the procedure described in Example 93, *trans*-(-aminomethyl-cyclohexyl)-carbamic acid benzylester hydrochloride (6.0 g), diisopropylethylamine (8.5 ml) and 2-methoxy-benzoylchloride (2.7 ml) are reacted together to give {4-[(2-methoxy-benzoylamino)-methyl]-cyclohexyl}-carbamic acid benzylester as white crystals melting at 150-152 °C: Rf(A7) 0.30.

c) trans-4-(Amino-cyclohexylmethyl)-2-methoxy-benzamide

A suspension of {4-[(2-methoxy-benzoylamino)-methyl]-cyclohexyl}-carbamic acid benzylester (5.75 g) and 10% Pd/C (0.5 g) in methanol (300 ml) is hydrogenated under atmospheric pressure at room temperature for 6 h. The catalyst is filtered off over Celite and the filtrate is concentrated *in vacuo* to give *trans*-4-(amino-cyclohexylmethyl)-2-methoxy-benzamide as white crystals melting at 59-61 °C: Rf(G1) 0.06.

In analogous manner as described hereinbefore following compound can be prepared:

Example 99: N-trans-4-[4-(Cyclopropylmethylamino)-quinazolin-2-ylamino]-cyclohexylmethyl)-2-methoxy-benzamide hydrochloride

182-184 °C, Rf(H1) 0.41, ESI-MS: (M+H)<sup>+</sup> = 460.

Example 100: trans-4-(4-Chloro-phenylamino)-2-(4-methylaminomethyl-cyclohexyl)-quinazoline-2,4-diamine

To a suspension of lithium aluminum hydride (2.5 g) in THF is added under an inert atmosphere of nitrogen a solution of *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester (2.41 g) in THF (60 ml) below 10 °C. The mixture is heated at reflux for 5 h. After cooling to 0 °C, a mixture of THF and water is added followed by aqueous 4N NaOH solution and water. The resulting suspension is stirred for 1 h at room temperature. After the addition of magnesium sulfate and Celite the inorganic salts are removed by filtration. The filtrate is concentrated and the crude product is purified by chromatography (silica gel, B2-B5) to give *trans*-4-(4-chloro-phenylamino)-2-(4-methylaminomethyl-cyclohexyl)-quinazoline-2,4-diamine as an amorphous solid: Rf(D2) 0.36, ESI-MS: (M+H)<sup>+</sup> = 396, 398.

Example 101: trans-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-N-methyl-acetamide

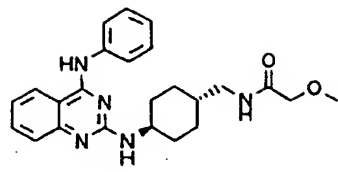
According to the procedure described in Example 96, *trans*-4-(4-chloro-phenylamino)-2-(4-methylaminomethyl-cyclohexyl)-quinazoline-2,4-diamine (0.2 g), diisopropylethylamine (0.12 g) and acetic anhydride (0.06 g) are reacted together to yield *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-N-methyl-acetamide as an amorphous solid: Rf(D1) 0.43, ESI-MS: (M+H)<sup>+</sup> = 438, 440.

In analogous manner as described hereinbefore following compound can be prepared:

Example 102: trans-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-N-methyl-benzamide

157-160 °C, Rf(H1) 0.46, ESI-MS: (M+H)<sup>+</sup> = 500, 502.

Example 103: trans-2-Methoxy-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide



According to the procedure described in Example 78, 2-chloro-4-(4-chloro-phenyl)-amino-quinazoline (2.6 g) and *trans*-(4-amino-cyclohexylmethyl)-2-methoxy-acetamide (2 g) are reacted together to give *trans*-2-methoxy-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide as white crystals melting at 204-210 °C: Rf(H1) 0.46, ESI-MS: (M+H)<sup>+</sup> = 420.

The starting material can be prepared, for example, as follows:

a) *trans*-{4-[(2-Methoxy-acetyl-amino)-methyl]-cyclohexyl}-carbamic acid benzylester

According to the procedure described in Example 98b, *trans*-(-aminomethyl-cyclohexyl)-carbamic acid benzylester hydrochloride (Example 98a) (8.0 g), diisopropylethylamine (12 ml) and methoxy-acetylchloride (2.7 ml) are reacted together to give *trans*-{4-[(2-methoxy-acetyl-amino)-methyl]-cyclohexyl}-carbamic acid benzylester as white crystals melting at 167-169 °C: Rf(H1) 0.45, ESI-MS: (M+H)<sup>+</sup> = 335.

b) *trans*-(4-amino-cyclohexylmethyl)-2-methoxy-acetamide

According to the procedure described in Example 98c, *trans*-{4-[(2-methoxy-acetyl-amino)-methyl]-cyclohexyl}-carbamic acid benzylester (5.75 g) and 10% Pd/C (0.5 g) are hydrogenated to give *trans*-(4-amino-cyclohexylmethyl)-2-methoxy-acetamide as a light yellow waxy solid: Rf(D2) 0.31, ESI-MS: (M+H)<sup>+</sup> = 201.

In analogous manner as described hereinbefore following compounds can be prepared:

Example 104: *trans*-2-Methoxy-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide hydrochloride

149-152 °C, Rf(H1) 0.41.

Example 105: trans-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester hydrochloride

207-210 °C, Rf(D2) 0.34, FAB-MS: (M+H)<sup>+</sup> = 478.

Example 106: trans-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-methanesulfonamide hydrochloride

177-182 °C, FAB-MS: (M+H)<sup>+</sup> = 456.

Example 107: trans-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-(N,N-dimethylamino)-sulfonamide hydrochloride

258-261 °C, Rf(H1) 0.42, FAB-MS: (M+H)<sup>+</sup> = 485.

Example 108: trans-4-(Cyclopropylmethyl)-2-(4-piperidin-1-ylmethyl-cyclohexyl)-quinazoline-2,4-diamine dihydrochloride

Rf(D2) 0.13.

Example 109: trans-4-(4-Chloro-phenyl)-2-(4-piperidin-1-ylmethyl-cyclohexyl)-quinazoline-2,4-diamine dihydrochloride

Rf(D2) 0.12.

Example 110: 4-(3-Chloro-phenyl)-2-cyclohexyl-quinazoline-2,4-diamine hydrochloride

According to the procedure described in Example 78, 2-chloro-4-(3-chloro-phenyl)-amino-quinazoline (0.435 g) and cyclohexylamine (0.17 ) are reacted together to give 4-(3-chloro-phenyl)-2-cyclohexyl-quinazoline-2,4-diamine hydrochloride as a white powder melting at 237-240 °C: Rf(H1) 0.56.

In analogous manner as described hereinbefore following compounds can be prepared:

Example 111: 2-(N-Methyl-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride

M.p. 269 - 270 °C.

Example 112: 2-(N-Methyl-cyclohexylamino)-8-hydroxy-4-phenylamino-quinazoline hydrochloride

Rf(A1) 0.82.

Example 113: 2-(N-Methyl-cyclohexylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride

Rf(A1) 0.46.

Example 114: 2-(N-Methyl-cyclohexylamino)-8-(methoxycarbonyl-methoxy)-4-phenylamino-quinazoline hydrochloride

M.p. 192 - 193 °C.

Example 115: 2-(N-Methyl-cyclohexylamino)-8-[(2-hydroxy-ethoxy)]-4-phenylamino-quinazoline hydrochloride

M.p. 232 - 234 °C.

Example 116: 2-(N-Methyl-cyclohexylamino)-8-hydroxy-4-(4-fluoro-phenylamino)-quinazoline hydrochloride

M.p. 285 - 286 °C.

Example 117: 2-(N-Ethyl-cyclohexylamino)-8-hydroxy-4-(4-chloro-phenylamino)-quinazoline hydrochloride

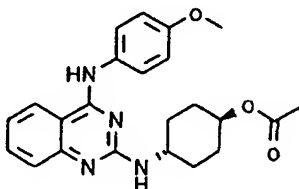
Rf(A1) 0.91.

Example 118: trans-2-(4-Benzoyloxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride



M.p. 238 - 239 °C.

Example 119: *trans*-2-(4-Acetoxy-cyclohexylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride



M.p. 168 - 169 °C.

Example 120: N(2)-(trans-4-Dimethylamino-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine

According to the procedure described in Example 78, *trans*-(4-aminomethyl-cyclohexyl)-dimethyl-amine bis(trifluoroacetic acid) (0.556 g), (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine (0.286 g) and ethyldiisopropylamine (0.36 ml) are reacted together to give N(2)-(trans-4-dimethylamino-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine as a foam melting at 97-103 °C. R<sub>f</sub>(C3) 0.15; ESI-MS: (M+H)<sup>+</sup>=404.

The starting material can be prepared, for example, as follows:

a) 4-Amino-4'-methyl-biphenyl-3-carboxylic acid

A solution of cesium carbonate (127.3 g) in degassed water (145 ml) is added to a suspension of 2-amino-5-bromo-benzoic acid (60 g) in toluene (1000 ml) at room temperature under an inert atmosphere of argon. *p*-Tolylboronic acid (49.1 g) and tetrakis(triphenylphosphine)palladium(0) (4.5 g) are added and the mixture is heated at reflux for 18 h. Water is added (500 ml) to the cooled reaction mixture and the organic phase is extracted with water. The combined aqueous phases are treated with activated charcoal and filtered through Celite. The filtrate is acidified with 4N HCl and the resulting suspension is extracted with ethyl acetate. The combined organic extracts are washed with brine, dried over magnesium sulfate, treated with activated charcoal, filtered, and

concentrated to ca. 400 ml. The resulting crystals are filtered and dried to give 4-amino-4'-methyl-biphenyl-3-carboxylic acid. Rf(B2) 0.62.

b) 6-*p*-Tolyl-quinazoline-2,4-diol

According to the procedure described in Example 127a, 4-amino-4'-methyl-biphenyl-3-carboxylic acid (36.4 g) is converted into 6-*p*-tolyl-quinazoline-2,4-diol. Rf(B2) 0.70; ESI-MS: (M+H)<sup>+</sup>=253.

c) 2,4-Dichloro-6-*p*-tolyl-quinazoline

According to the procedure described in Example 127b, 6-*p*-tolyl-quinazoline-2,4-diol (37.8 g) is converted into 2,4-dichloro-6-*p*-tolyl-quinazoline melting at 122-124 °C. Rf(A11) 0.27.

d) (2-Chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine

According to the procedure described in Example 40a, 2,4-dichloro-6-*p*-tolyl-quinazoline (9.1 g) and methylamine (10 ml) in ethanol (100 ml) are reacted together to give (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine as white crystals melting at 277-278 °C. Rf(B2) 0.22; ESI-MS: (M+H)<sup>+</sup>=284,286.

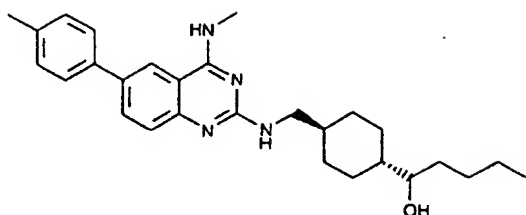
e) *trans*-(4-Dimethylamino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester

A mixture of *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (Example 90b) (1.05 g), 36.5% aqueous formaldehyde (0.8 ml) and 10% Pd/C (200 mg) in methanol (25 ml) and water (5 ml) is hydrogenated under 1 atmosphere of hydrogen. After 4 h, the catalyst is filtered off and the filtrate concentrated to give *trans*-(4-dimethylamino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester as a pale yellow oil which solidified on standing. Rf(D1) 0.23; ESI-MS: (M+H)<sup>+</sup>=257.

f) *trans*-(4-Aminomethyl-cyclohexyl)-dimethyl-amine bis(trifluoroacetic acid)

Reaction of *trans*-(4-dimethylamino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (1.11 g) and trifluoroacetic acid (5 ml) gives the *trans*-(4-aminomethyl-cyclohexyl)-dimethyl-amine bis(trifluoroacetic acid) salt, which is used without further purification.

Example 121: 1-{*trans*-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-ol



According to the procedure described in Example 78, 1-(*trans*-4-aminomethyl-cyclohexyl)-pentan-1-ol (0.199 g) and (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine (0.284 g) are reacted together to give 1-{*trans*-4-[(4-methylamino-6-*p*-tolyl-quinazolin-2-ylamino)-methyl]-cyclohexyl}-pentan-1-ol as a foam: Rf(C5) 0.43; ESI-MS: (M+H)<sup>+</sup>=447.

The starting materials can be prepared, for example, as follows:

a) *trans*-(4-Formyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester

A mixture of "wet" dichloromethane (100 ml, containing 0.41 ml of water) is added over 20 min to a suspension of *trans*-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (5 g) (Example 11a) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (13.1 g) in dichloromethane (50 ml) at room temperature. After 15 min, the reaction mixture is diluted with diethylether, washed with 1:1 10% aqueous sodium thiosulfate/saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated to give *trans*-(4-formyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester as a light yellow oil which is used without further purification. Rf(A1) 0.57.

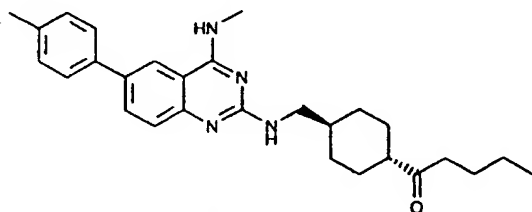
b) [*trans*-4-(1-Hydroxy-pentyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester

A solution of *trans*-(4-formyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (4.95 g) in THF (40 ml) is added dropwise to a 0.7M solution of butylmagnesium chloride in THF (60 ml) at -78 °C. Additional THF (70 ml) is added to aid stirring. After 1 h, the reaction mixture is quenched with saturated aqueous ammonium chloride, diluted with water and extracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate and concentrated. Chromatography on silica gel (A4 then A1) yields [*trans*-4-(1-hydroxy-pentyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester as a white solid. Rf(A1) 0.60; ESI-MS: (M+H)<sup>+</sup>=300.

c) 1-(*trans*-4-Aminomethyl-cyclohexyl)-pentan-1-ol

Reaction of [*trans*-4-(1-hydroxy-pentyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (3.02 g) and trifluoroacetic acid (25 ml) according to the procedure described in Example 120f gives the crude trifluoroacetic acid salt. The residue is dissolved in dichloromethane and washed with 1N NaOH. The aqueous phase is saturated with sodium chloride and extracted with dichloromethane. The combined organic phases are washed with brine, dried over magnesium sulfate and concentrated to give 1-(*trans*-4-aminomethyl-cyclohexyl)-pentan-1-ol, which is used without further purification. Rf(C5) 0.21; ESI-MS: (M+H)<sup>+</sup>=200.

Example 122: 1-{*trans*-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-one



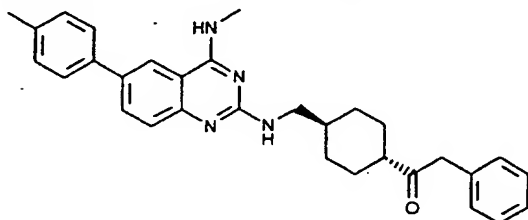
A mixture of "wet" dichloromethane (1.11 ml containing 0.003 ml of water) is added to a suspension of 1-{*trans*-4-[(4-methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-ol (0.072 g) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (0.103 g) in dichloromethane (0.5 ml) at room temperature. After 2 h, an additional amount of Dess-Martin periodinane (0.068 g) in dichloromethane (1.5 ml) is added. After 5 h, the reaction mixture is diluted with dichloromethane, washed with 1:1 10% aqueous sodium thiosulfate/saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated. Chromatography on silica gel (B1 then C10) yields 1-{*trans*-4-[(4-methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-one as a solid melting at 193-198 °C. Rf(C5) 0.44; ESI-MS: (M+H)<sup>+</sup>=445.

In analogous manner as described hereinbefore following compound can be prepared:

Example 123: {*trans*-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-phenyl-methanol

Rf(C10) 0.34; ESI-MS: (M+H)<sup>+</sup>=467.

Example 124: 1-{*trans*-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2-ylamino)-methyl]-cyclohexyl}-2-phenyl-ethanone



Rf(C10) 0.39; ESI-MS: (M+H)<sup>+</sup>=479.

Example 125: N(2)-(trans-4-Ethanesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine

3-Chloroperoxybenzoic acid (0.188 g, ca. 55%) is added to a solution of N(2)-(trans-4-ethylsulfonylmethyl-cyclohexylmethyl)-N4-methyl-6-*p*-tolyl-quinazoline-2,4-diamine (0.1 g) in dichloromethane (4 ml) at -78 °C. After 1 h, the mixture is warmed to room temperature and stirred an additional 2 h. The reaction mixture is diluted with dichloromethane and washed with 1N NaOH and brine and the organic phase is dried over sodium sulfate and concentrated. Chromatography on silica gel (C8) yields N(2)-(trans-4-ethanesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine as a solid melting at 99-103 °C. Rf(C8) 0.37; ESI-MS: (M+H)<sup>+</sup>=467.

The starting material can be prepared, for example, as follows:

a) Toluene-4-sulfonic acid 4-trans-(tert-butoxycarbonylamino-methyl)-cyclohexylmethyl ester

A solution of *p*-toluenesulfonyl chloride (20.6 g) in pyridine (50 ml) is added to a solution of trans-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (Example 11a) (20 g) in pyridine (160 ml) at 0 °C, and the reaction mixture is allowed to warm to room temperature. 4Å molecular sieves are added after 22 h and the reaction is stirred a further 5 h. The mixture is filtered, concentrated and the residue is then partitioned between ethyl acetate and water. The organic phase is washed with water, 10% aqueous citric acid and brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (A9

then A10) yields toluene-4-sulfonic acid 4-*trans*-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl ester as a white solid. Rf(A1) 0.74.

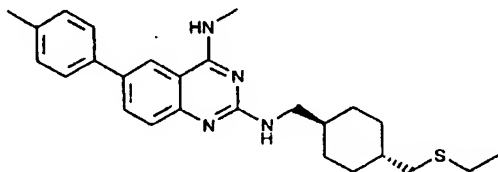
b) (*trans*-4-Ethylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester

A solution of toluene-4-sulfonic acid 4-*trans*-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl ester (10 g) in N,N-dimethylformamide (70 ml) is added to a suspension of ethanethiol sodium salt (4.68 g) in N,N-dimethylformamide (80 ml) at room temperature, and the reaction mixture is then heated to 50 °C. After 5 h, the reaction is concentrated and the residue is partitioned between ethyl acetate and water. The aqueous phase is re-extracted with ethyl acetate and the combined organic phases are washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (A5) yields (*trans*-4-ethylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester as a solid. Rf(A4) 0.70; ESI-MS: (M+H)<sup>+</sup>=288.

c) (*trans*-4-Ethylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid

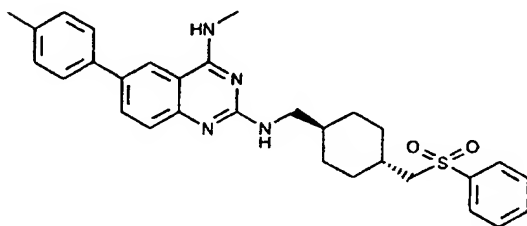
Trifluoroacetic acid (15 ml) is added dropwise to a solution of (*trans*-4-ethylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (1.51 g) in dichloromethane (30 ml) at 0 °C. The reaction mixture is worked up after 4.5 h by concentrating to give (*trans*-4-ethylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid which is used without further purification. Rf(C5) 0.42; ESI-MS: (M+H)<sup>+</sup>=188.

d) N(2)-(trans-4-Ethylsulfanylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine



According to the procedure described in Example 78, (*trans*-4-ethylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid (0.433 g), (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine (0.285 g) and ethyldiisopropylamine (0.18 ml) are reacted together to give N(2)-(trans-4-ethylsulfanylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine as a foam: Rf(C8) 0.46; ESI-MS: (M+H)<sup>+</sup>=435.

Example 126: N(2)-(trans-4-Benzenesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine



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According to the procedure described in Example 124, N(2)-(trans-4-phenylsulfanylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine (0.1 g) and 3-Chloroperoxybenzoic acid (0.164 g, ca. 55%) are reacted together to give N(2)-(trans-4-benzenesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine: Rf(C1) 0.16; ESI-MS: (M+H)<sup>+</sup>=515.

The starting material can be prepared, for example, as follows:

a) (trans-4-Phenylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester

Reaction of toluene-4-sulfonic acid 4-*trans*-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl ester (10 g) and thiophenol sodium salt (7.2 g) followed by chromatography (silica gel, B10 then B9) yields (trans-4-phenylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester as a solid. Rf(A4) 0.66; ESI-MS: (M+H)<sup>+</sup>=336.

b) (trans-4-Phenylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid

Reaction of (trans-4-phenylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (1.52 g) and trifluoroacetic acid (30 ml) gives the (trans-4-phenylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid salt, which is used without further purification. Rf(C5) 0.40; ESI-MS: (M+H)<sup>+</sup>=236.

c) N(4)-Methyl-N(2)-(trans-4-phenylsulfanylmethyl-cyclohexylmethyl)-6-*p*-tolyl-quinazoline-2,4-diamine

According to the procedure described in Example 78, (trans-4-phenylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid (0.351 g), (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine (0.284 g) and ethyldiisopropylamine (0.18 ml) are reacted together to give N(4)-methyl-N(2)-(trans-4-phenylsulfanylmethyl-cyclohexylmethyl)-6-*p*-tolyl-quinazoline-2,4-diamine as a foam: Rf(B2) 0.42; ESI-MS: (M+H)<sup>+</sup>=483.

Example 127: 1-(trans-4-[[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-pentan-1-ol

According to the procedure described in Example 56, 1-(trans-4-aminomethyl-cyclohexyl)-pentan-1-ol (0.239 g), N-(2-chloro-6,8-dimethyl-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine (0.357 g) and ethyldiisopropylamine (0.53 ml) are reacted together to give 1-(trans-4-[[4-(3-diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-pentan-1-ol: Rf(C9) 0.67; ESI-MS: (M+H)<sup>+</sup>=484.

The starting material can be prepared, for example, as follows:

a) 6,8-Dimethyl-quinazoline-2,4-diol

To a suspension of 3,5-dimethylantranilic acid (49.86 g) in dioxane (400 ml) is added acetic acid (18.7 ml) and water (300 ml) at 10 °C. A solution of potassium isocyanate (26.66 g) in water (50 ml) is added dropwise over 15 min, and the reaction mixture is stirred at room temperature for 4.5 h. NaOH pellets (160.9 g) are added all at once and the suspension is heated to reflux for 1.5 h. The reaction mixture is acidified by the dropwise addition of concentrated aqueous HCl and filtered. The solid is washed with water, triturated with acetone and methyl *tert*-butyl ether, and then dried under vacuum to give 6,8-dimethyl-quinazoline-2,4-diol as an amorphous solid. Rf(A4) 0.09; ESI-MS: (M-H)<sup>-</sup>=189.

b) 2,4-Dichloro-6,8-dimethyl-quinazoline

To a mixture of phosphorus oxychloride (115 ml) and phosphorus pentachloride (23 g) are added 6,8-dimethyl-quinazoline-2,4-diol (25 g) at room temperature. The resulting suspension is heated under reflux for 14 h, cooled to room temperature, diluted with toluene (700 ml) and then poured into water. The mixture is stirred for 20 min, filtered and then the



liquid phases are separated. The organic phase is washed with water, 1N aqueous sodium carbonate and brine, dried over magnesium sulfate and concentrated in vacuo to give 2,4-dichloro-6,8-dimethyl-quinazoline as a solid melting at 140-143 °C. Rf(A4) 0.72.

c) N-(2-Chloro-6,8-dimethyl-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride

The reaction of 2,4-dichloro-6,8-dimethyl-quinazoline (2.79 g) and 3-diethylamino-propylamine according to the procedure described in Example 56a gives N-(2-chloro-6,8-dimethyl-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride as a solid melting at 159-161 °C. Rf(C8) 0.30; ESI-MS: (M+H)<sup>+</sup>=321, 323.

Example 128: 1-(trans-4-[[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-pentan-1-one

According to the procedure described in Example 122, 1-(trans-4-[[4-(3-diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-pentan-1-ol (0.094 g) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (0.201 g) are reacted together to give 1-(trans-4-[[4-(3-diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-pentan-1-one: Rf(C5) 0.27; ESI-MS: (M+H)<sup>+</sup>=482.

Example 129: 1-(trans-4-[[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-2-phenyl-ethanone

Rf(C10) 0.31; ESI-MS: (M+H)<sup>+</sup>=516.

In analogous manner as described hereinbefore following compound can be prepared:

Example 130: (trans-4-[[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-phenyl-methanone

Rf(C10) 0.35; ESI-MS: (M+H)<sup>+</sup>=502.

Example 131:

Tablets, each containing 50 mg of active ingredient, for example, 2-cyclohexylamino-4-phenylamino-quinazoline hydrochloride, can be prepared as follows:

Composition (for 10,000 tablets)

Active ingredient	500.0 g
Lactose	500.0 g
Potato starch	352.0 g
Gelatin	8.0 g
Talc	60.0 g
Magnesium stearate	10.0 g
Silica (highly disperse)	20.0 g
Ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch, and the mixture is moistened using an alcoholic solution of the gelatin and granulated by means of a sieve. After drying, the remainder of the potato starch, the talc, the magnesium stearate and the highly disperse silica are admixed and the mixture is compressed to give tablets of weight 145.0 mg each and active ingredient content 50.0 mg which, if desired, can be provided with breaking notches for finer adjustment of the dose.

Example 132: Coated tablets, each containing 100 mg of active ingredient, for example, 2-cyclohexylamino-4-phenylamino-quinazoline hydrochloride, can be prepared as follows:

Composition (for 1000 tablets):

Active ingredient	100.00 g
Lactose	100.00 g
Corn starch	70.00 g
Talc	8.50 g
Calcium stearate	1.50 g
Hydroxypropylmethylcellulose	2.36 g
Shellac	0.64 g
Water q.s.	
Dichloromethane	q.s.

- 131 -

The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened and granulated with a paste prepared from 15 g of corn starch and water (with warming). The granules are dried, and the remainder of the corn starch, the talc and the calcium stearate are added and mixed with the granules. The mixture is compressed to give tablets (weight: 280 mg) and these are coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of the coated tablet: 283 mg).

Example 133: Tablets and coated tablets containing another compound of the formula (I) or a pharmaceutically acceptable salt of a compound of the formula (I), for example as in one of Examples 1 to 130, can also be prepared in an analogous manner to that described in Examples 131 and 132.

- 132 -

## SEQUENCE LISTING

## (1) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1501 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (iii) HYPOTHETICAL: NO

## (iv) ANTI-SENSE: NO

## (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 61..1432

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TTAGTTTTGT TCTGAGAACG TTAGAGTTAT AGTACCGTGC GATCGTTCTT  
CAAGCTGCTA 60

ATG GAC GTC CTC TTC TTC CAC CAG GAT TCT AGT ATG GAG TTT AAG CTT 108  
Met Asp Val Leu Phe Phe His Gln Asp Ser Ser Met Glu Phe Lys Leu

- 133 -

1 5 10 15

GAG GAG CAT TTT AAC AAG ACA TTT GTC ACA GAG AAC AAT ACA GCT GCT 156

Glu Glu His Phe Asn Lys Thr Phe Val Thr Glu Asn Asn Thr Ala Ala

20 25 30

GCT CGG AAT GCA GCC TTC CCT GCC TGG GAG GAC TAC AGA GGC AGC GTA

204

Ala Arg Asn Ala Ala Phe Pro Ala Trp Glu Asp Tyr Arg Gly Ser Val

35 40 45

GAC GAT TTA CAA TAC TTT CTG ATT GGG CTC TAT ACA TTC GTA AGT CTT 252

Asp Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu

50 55 60

CTT GGC TTT ATG GGC AAT CTA CTT ATT TTA ATG GCT GTT ATG AAA AAG 300

Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Val Met Lys Lys

65 70 75 80

CGC AAT CAG AAG ACT ACA GTG AAC TTT CTC ATA GGC AAC CTG GCC TTC

348

Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe

85 90 95

TCC GAC ATC TTG GTC GTC CTG TTT TGC TCC CCT TTC ACC CTG ACC TCT 396

Ser Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser

100 105 110

GTC TTG TTG GAT CAG TGG ATG TTT GGC AAA GCC ATG TGC CAT ATC ATG 444

Val Leu Leu Asp Gln Trp Met Phe Gly Lys Ala Met Cys His Ile Met

115 120 125

CCG TTC CTT CAA TGT GTG TCA GTT CTG GTT TCA ACT CTG ATT TTA ATA 492

- 134 -

Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile

130 135 140

TCA ATT GCC ATT GTC AGG TAT CAT ATG ATA AAG CAC CCT ATT TCT AAC 540

Ser Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn

145 150 155 160

AAT TTA ACG GCA AAC CAT GGC TAC TTC CTG ATA GCT ACT GTC TGG ACA 588

Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr

165 170 175

CTG GGC TTT GCC ATC TGT TCT CCC CTC CCA GTG TTT CAC AGT CTT GTG 636

Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val

180 185 190

GAA CTT AAG GAG ACC TTT GGC TCA GCA CTG CTG AGT AGC AAA TAT CTC

684

Glu Leu Lys Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Lys Tyr Leu

195 200 205

TGT GTT GAG TCA TGG CCC TCT GAT TCA TAC AGA ATT GCT TTC ACA ATC 732

Cys Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile

210 215 220

TCT TTA TTG CTA GTG CAG TAT ATC CTG CCT CTA GTA TGT TTA ACG GTA 780

Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val

225 230 235 240

AGT CAT ACC AGC GTC TGC CGA AGC ATA AGC TGT GGA TTG TCC CAC AAA

828

Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser His Lys

245 250 255

- 135 -

GAA AAC AGA CTC GAA GAA AAT GAG ATG ATC AAC TTA ACC CTA CAG CCA

876

Glu Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu Gln Pro

260

265

270

TCC AAA AAG AGC AGG AAC CAG GCA AAA ACC CCC AGC ACT CAA AAG TGG

924

Ser Lys Lys Ser Arg Asn Gln Ala Lys Thr Pro Ser Thr Gln Lys Trp

275

280

285

AGC TAC TCA TTC ATC AGA AAG CAC AGA AGG AGG TAC AGC AAG AAG ACG

972

Ser Tyr Ser Phe Ile Arg Lys His Arg Arg Tyr Ser Lys Lys Thr

290

295

300

GCC TGT GTC TTA CCC GCC CCA GCA GGA CCT TCC CAG GGG AAG CAC CTA

1020

Ala Cys Val Leu Pro Ala Pro Ala Gly Pro Ser Gln Gly Lys His Leu

305

310

315

320

GCC GTT CCA GAA AAT CCA GCC TCC GTC CGT AGC CAG CTG TCG CCA TCC

1068

Ala Val Pro Glu Asn Pro Ala Ser Val Arg Ser Gln Leu Ser Pro Ser

325

330

335

AGT AAG GTC ATT CCA GGG GTC CCA ATC TGC TTT GAG GTG AAA CCT GAA

1116

Ser Lys Val Ile Pro Gly Val Pro Ile Cys Phe Glu Val Lys Pro Glu

340

345

350

GAA AGC TCA GAT GCT CAT GAG ATG AGA GTC AAG CGT TCC ATC ACT AGA

1164

Glu Ser Ser Asp Ala His Glu Met Arg Val Lys Arg Ser Ile Thr Arg

- 136 -

355                    360                    365

ATA AAA AAG AGA TCT CGA AGT GTT TTC TAC AGA CTG ACC ATA CTG ATA    1212  
Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile

370                    375                    380

CTC GTG TTC GCC GTT AGC TGG ATG CCA CTC CAC GTC TTC CAC GTG GTG  
1260  
Leu Val Phe Ala Val Ser Trp Met Pro Leu His Val Phe His Val Val

385                    390                    395                    400

ACT GAC TTC AAT GAT AAC TTG ATT TCC AAT AGG CAT TTC AAG CTG GTA    1308  
Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val

405                    410                    415

TAC TGC ATC TGT CAC TTG TTA GGC ATG ATG TCC TGT TGT CTA AAT CCG    1356  
Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro

420                    425                    430

ATC CTA TAT GGT TTC CTT AAT AAT GGT ATC AAA GCA GAC TTG AGA GCC    1404  
Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Arg Ala

435                    440                    445

CTT ATC CAC TGC CTA CAC ATG TCA TGA TTCTCTCTGTG CACCAAAGAG    1452  
Leu Ile His Cys Leu His Met Ser \*

450                    455

AGAAGAAACG TGGTAATTGA CACATAATTT ATACAGAAGT ATTCTGGAT  
1501

(2) INFORMATION FOR SEQ ID NO:2:



- 137 -

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Asp Val Leu Phe Phe His Gln Asp Ser Ser Met Glu Phe Lys Leu

1            5            10            15

Glu Glu His Phe Asn Lys Thr Phe Val Thr Glu Asn Asn Thr Ala Ala

20            25            30

Ala Arg Asn Ala Ala Phe Pro Ala Trp Glu Asp Tyr Arg Gly Ser Val

35            40            45

Asp Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu

50            55            60

Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Val Met Lys Lys

65            70            75            80

Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe

85            90            95

Ser Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser

100            105            110

Val Leu Leu Asp Gln Trp Met Phe Gly Lys Ala Met Cys His Ile Met

115            120            125

- 138 -

Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile  
130 135 140

Ser Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn  
145 150 155 160

Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr  
165 170 175

Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val  
180 185 190

Glu Leu Lys Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Lys Tyr Leu  
195 200 205

Cys Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile  
210 215 220

Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val  
225 230 235 240

Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser His Lys  
245 250 255

Glu Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu Gln Pro  
260 265 270

Ser Lys Lys Ser Arg Asn Gln Ala Lys Thr Pro Ser Thr Gln Lys Trp  
275 280 285

Ser Tyr Ser Phe Ile Arg Lys His Arg Arg Arg Tyr Ser Lys Lys Thr  
290 295 300

- 139 -

Ala Cys Val Leu Pro Ala Pro Ala Gly Pro Ser Gln Gly Lys His Leu  
305                    310                    315                    320

Ala Val Pro Glu Asn Pro Ala Ser Val Arg Ser Gln Leu Ser Pro Ser  
                  325                    330                    335

Ser Lys Val Ile Pro Gly Val Pro Ile Cys Phe Glu Val Lys Pro Glu  
                  340                    345                    350

Glu Ser Ser Asp Ala His Glu Met Arg Val Lys Arg Ser Ile Thr Arg  
                  355                    360                    365

Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile  
                  370                    375                    380

Leu Val Phe Ala Val Ser Trp Met Pro Leu His Val Phe His Val Val  
385                    390                    395                    400

Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val  
                  405                    410                    415

Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro  
                  420                    425                    430

Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Arg Ala  
                  435                    440                    445

Leu Ile His Cys Leu His Met Ser \*  
                  450                    455

(3) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- 140 -

- (A) LENGTH: 1457 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 61..1432

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

GTTTCCCTCT GAATAGATTA ATTTAAAGTA GTCATGTAAT GTTTTTTTGG  
TTGCTGACAA 60

ATG TCT TTT TAT TCC AAG CAG GAC TAT AAT ATG GAT TTA GAG CTC GAC 108  
Met Ser Phe Tyr Ser Lys Gln Asp Tyr Asn Met Asp Leu Glu Leu Asp  
1 5 10 15

GAG TAT TAT AAC AAG ACA CTT GCC ACA GAG AAT AAT ACT GCT GCC ACT 156  
Glu Tyr Tyr Asn Lys Thr Leu Ala Thr Glu Asn Asn Thr Ala Ala Thr  
20 25 30

CGG AAT TCT GAT TTC CCA GTC TGG GAT GAC TAT AAA AGC AGT GTA GAT 204  
Arg Asn Ser Asp Phe Pro Val Trp Asp Asp Tyr Lys Ser Ser Val Asp  
35 40 45

- 141 -

GAC TTA CAG TAT TTT CTG ATT GGG CTC TAT ACA TTT GTA AGT CTT CTT 252

Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu

50 55 60

GGC TTT ATG GGG AAT CTA CTT ATT TTA ATG GCT CTC ATG AAA AAG CGT 300

Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Leu Met Lys Lys Arg

65 70 75 80

AAT CAG AAG ACT ACG GTA AAC TTC CTC ATA GGC AAT CTG GCC TTT TCT 348

Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser

85 90 95

GAT ATC TTG GTT GTG CTG TTT TGC TCA CCT TTC ACA CTG ACG TCT GTC 396

Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val

100 105 110

TTG CTG GAT CAG TGG ATG TTT GGC AAA GTC ATG TGC CAT ATT ATG CCT 444

Leu Leu Asp Gln Trp Met Phe Gly Lys Val Met Cys His Ile Met Pro

115 120 125

TTT CTT CAA TGT GTG TCA GTT TTG GTT TCA ACT TTA ATT TTA ATA TCA 492

Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser

130 135 140

ATT GCC ATT GTC AGG TAT CAT ATG ATA AAA CAT CCC ATA TCT AAT AAT 540

Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn Asn

145 150 155 160

TTA ACA GCA AAC CAT GGC TAC TTT CTG ATA GCT ACT GTC TGG ACA CTA 588

Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu

165 170 175

- 142 -

GGT TTT GCC ATC TGT TCT CCC CTT CCA GTG TTT CAC AGT CTT GTG GAA 636

Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val Glu

180

185

190

CTT CAA GAA ACA TTT GGT TCA GCA TTG CTG AGC AGC AGG TAT TTA TGT 684

Leu Gln Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Arg Tyr Leu Cys

195

200

205

GTT GAG TCA TGG CCA TCT GAT TCA TAC AGA ATT GCC TTT ACT ATC TCT 732

Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser

210

215

220

TTA TTG CTA GTT CAG TAT ATT CTG CCC TTA GTT TGT CTT ACT GTA AGT 780

Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser

225

230

235

240

CAT ACA AGT GTC TGC AGA AGT ATA AGC TGT GGA TTG TCC AAC AAA GAA 828

His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser Asn Lys Glu

245

250

255

AAC AGA CTT GAA GAA AAT GAG ATG ATC AAC TTA ACT CTT CAT CCA TCC 876

Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser

260

265

270

AAA AAG AGT GGG CCT CAG GTG AAA CTC TCT GGC AGC CAT AAA TGG AGT

924

Lys Lys Ser Gly Pro Gln Val Lys Leu Ser Gly Ser His Lys Trp Ser

275

280

285

TAT TCA TTC ATC AAA AAA CAC AGA AGA AGA TAT AGC AAG AAG ACA GCA 972

Tyr Ser Phe Ile Lys Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala

290

295

300

- 143 -

TGT GTG TTA CCT GCT CCA GAA AGA CCT TCT CAA GAG AAC CAC TCC AGA  
1020

Cys Val Leu Pro Ala Pro Glu Arg Pro Ser Gln Glu Asn His Ser Arg

305            310            315            320

ATA CTT CCA GAA AAC TTT GGC TCT GTA AGA AGT CAG CTC TCT TCA TCC    1068

Ile Leu Pro Glu Asn Phe Gly Ser Val Arg Ser Gln Leu Ser Ser Ser

325            330            335

AGT AAG TTC ATA CCA GGG GTC CCC ACT TGC TTT GAG ATA AAA CCT GAA  
1116

Ser Lys Phe Ile Pro Gly Val Pro Thr Cys Phe Glu Ile Lys Pro Glu

340            345            350

GAA AAT TCA GAT GTT CAT GAA TTG AGA GTA AAA CGT TCT GTT ACA AGA    1164

Glu Asn Ser Asp Val His Glu Leu Arg Val Lys Arg Ser Val Thr Arg

355            360            365

ATA AAA AAG AGA TCT CGA AGT GTT TTC TAC AGA CTG ACC ATA CTG ATA    1212

Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile

370            375            380

TTA GTA TTT GCT GTT AGT TGG ATG CCA CTA CAC CTT TTC CAT GTG GTA    1260

Leu Val Phe Ala Val Ser Trp Met Pro Leu His Leu Phe His Val Val

385            390            395            400

ACT GAT TTT AAT GAC AAT CTT ATT TCA AAT AGG CAT TTC AAG TTG GTG    1308

Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val

405            410            415

TAT TGC ATT TGT CAT TTG TTG GGC ATG ATG TCC TGT TGT CTT AAT CCA    1356

Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro

420            425            430

- 144 -

ATT CTA TAT GGG TTT CTT AAT AAT GGG ATT AAA GCT GAT TTA GTG TCC 1404

Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Val Ser

435

440

445

CTT ATA CAC TGT CTT CAT ATG TAA TAA TTCTCACTGT TTACCAAGGA 1452

Leu Ile His Cys Leu His Met \* \*

450

455

AAGAAC

1457

## (4) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Ser Phe Tyr Ser Lys Gln Asp Tyr Asn Met Asp Leu Glu Leu Asp

1

5

10

15

Glu Tyr Tyr Asn Lys Thr Leu Ala Thr Glu Asn Asn Thr Ala Ala Thr

20

25

30

Arg Asn Ser Asp Phe Pro Val Trp Asp Asp Tyr Lys Ser Ser Val Asp

35

40

45

Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu Leu

50

55

60



- 145 -

Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Leu Met Lys Lys Arg

65                      70                      75                      80

Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe Ser

85                      90                      95

Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser Val

100                      105                      110

Leu Leu Asp Gln Trp Met Phe Gly Lys Val Met Cys His Ile Met Pro

115                      120                      125

Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile Ser

130                      135                      140

Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn Asn

145                      150                      155                      160

Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr Leu

165                      170                      175

Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val Glu

180                      185                      190

Leu Gln Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Arg Tyr Leu Cys

195                      200                      205

Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile Ser

210                      215                      220

Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val Ser

225                      230                      235                      240

- 146 -

His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser Asn Lys Glu  
245 250 255

Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu His Pro Ser  
260 265 270

Lys Lys Ser Gly Pro Gln Val Lys Leu Ser Gly Ser His Lys Trp Ser  
275 280 285

Tyr Ser Phe Ile Lys Lys His Arg Arg Arg Tyr Ser Lys Lys Thr Ala  
290 295 300

Cys Val Leu Pro Ala Pro Glu Arg Pro Ser Gln Glu Asn His Ser Arg  
305 310 315 320

Ile Leu Pro Glu Asn Phe Gly Ser Val Arg Ser Gln Leu Ser Ser Ser  
325 330 335

Ser Lys Phe Ile Pro Gly Val Pro Thr Cys Phe Glu Ile Lys Pro Glu  
340 345 350

Glu Asn Ser Asp Val His Glu Leu Arg Val Lys Arg Ser Val Thr Arg  
355 360 365

Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile  
370 375 380

Leu Val Phe Ala Val Ser Trp Met Pro Leu His Leu Phe His Val Val  
385 390 395 400

Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val  
405 410 415

- 147 -

Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro

420

425

430

Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Val Ser

435

440

445

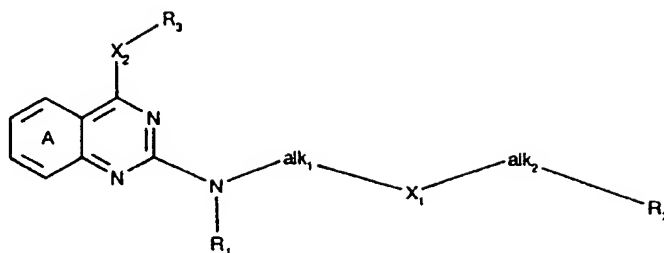
Leu Ile His Cys Leu His Met \* \*

450

455

What is claimed is

1. A compound of formula (I)



in which

alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent, a single bond or lower alkylene;

R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R<sub>2</sub> represents

- (i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, by carbamoyl, or by N-substituted carbamoyl;
- (ii) amino or substituted amino;
- (iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;
- (iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (v) carbamoyl or N-substituted carbamoyl;
- (vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is di-

substituted by lower alkylene {which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>} or which is disubstituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X<sub>3</sub>(X<sub>4</sub>)(X<sub>5</sub>) wherein, (a) if X<sub>3</sub> is -CH-, X<sub>4</sub> together with X<sub>5</sub> represent a structural element of formula -X<sub>6</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-X<sub>6</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>r</sub>-, or -(CH<sub>2</sub>)<sub>s</sub>-X<sub>6</sub>-CO-(CH<sub>2</sub>)<sub>t</sub>-; or, (b) if X<sub>3</sub> is -N-, X<sub>4</sub> together with X<sub>5</sub> represent a structural element of formula -CO-(CH<sub>2</sub>)<sub>u</sub>-; [X<sub>6</sub> being -CH<sub>2</sub>-, -N(R<sub>1</sub>)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X<sub>4</sub> is different from -CH<sub>2</sub>-];

X<sub>1</sub> represents C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene, C<sub>3</sub>-C<sub>8</sub>-cycloalkenylidene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene, or oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkenylidene;

X<sub>2</sub> represents -O-, -S(O)<sub>n</sub>- or a group of the formula -N(R<sub>4</sub>)-;

R<sub>3</sub> and R<sub>4</sub>, independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or  
 (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -S(O)<sub>n</sub>-R;

R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene [which may be interrupted by O, S(O)<sub>n</sub>, NR<sub>0</sub>] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;  
 (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-

lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, by C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-(O)<sub>v</sub>-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R<sub>0</sub> represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO<sub>2</sub>-R, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy; or a salt or a tautomer thereof.

2. A compound according to claim 1 of formula (I) or a salt or a tautomer thereof in which alk<sub>1</sub> and alk<sub>2</sub>, independently of one another, represent a single bond or lower alkylene; R<sub>1</sub> represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R<sub>2</sub> represents

- (i) hydrogen, halogen, lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by substituted amino, by lower alkoxy-carbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, or by substituted carbamoyl;
- (ii) amino or substituted amino;
- (iii) hydroxy, lower alkoxy, lower alkenyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxy-carbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl-oxy, or N-substituted aminocarbonyl-oxy;
- (iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (v) carbamoyl or N-substituted carbamoyl;
- (vi) a group selected from -CH(OH)-R, -CO-R, -NR<sub>1</sub>-CO-O-R, -NR<sub>1</sub>-CO-R, -NR<sub>1</sub>-CO-NR<sub>1</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-R, -NR<sub>1</sub>-SO<sub>2</sub>-NR<sub>1</sub>-R, -SO<sub>2</sub>-R, -SO<sub>2</sub>-NR<sub>1</sub>-R, or -SO<sub>2</sub>-NR<sub>1</sub>-CO-R, [R being as defined below and R<sub>1</sub> being as defined above, or the group -N(R)(R<sub>1</sub>) represents amino which is disubstituted by lower alkylene (which may be interrupted by O, S(O)<sub>n</sub> or NR<sub>0</sub>) or which is disubstituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or
- (vii) an element of formula -X<sub>3</sub>(X<sub>4</sub>)(X<sub>5</sub>) wherein, (a) if X<sub>3</sub> is -CH-, X<sub>4</sub> together with X<sub>5</sub> represent a structural element of formula -X<sub>6</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-X<sub>6</sub>-(CO)<sub>p</sub>-(CH<sub>2</sub>)<sub>r</sub>-, or -(CH<sub>2</sub>)<sub>s</sub>-X<sub>6</sub>-CO-(CH<sub>2</sub>)<sub>t</sub>-; or, (b) if X<sub>3</sub> is -N-, X<sub>4</sub> together with X<sub>5</sub> represent a structural element of formula -CO-(CH<sub>2</sub>)<sub>u</sub>-; [X<sub>6</sub> being -CH<sub>2</sub>-, -N(R<sub>1</sub>)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1 or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X<sub>4</sub> is different from -CH<sub>2</sub>-];

X<sub>1</sub> represents C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylene, oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkenylene, or oxo-C<sub>3</sub>-C<sub>8</sub>-cycloalkylidene;

X<sub>2</sub> represents -O-, -S(O)<sub>n</sub>- or a group of the formula -N(R<sub>4</sub>)-;

R<sub>3</sub> and R<sub>4</sub>, independently of one another, represent

- (i) hydrogen, lower alkyl, lower alkenyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, substituted carbamoyl, and -S(O)<sub>n</sub>-R;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ , or  $NR_0$ ] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

- (i) halogen, lower alkyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;
- (ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3$ - $C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;
- (iv) amino, substituted amino;
- (v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
- (vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety is derived and selected from the group consisting of phenyl, biphenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolinyl, or quinazolinyl;

wherein, in each case, the amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by  $C_3$ - $C_8$ -cycloalkyl, by  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O,  $S(O)_n$  or  $NR_0$ ] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by  $-CO-(O)_v-R$  and the integer v is 0 or 1;



wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case,  $R_0$  represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

3. A compound according to claim 1 of formula (I) or a salt or a tautomer thereof in which  $alk_1$  and  $alk_2$ , independently of one another, represent a single bond or lower alkylene;  $R_1$  represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;  $R_2$  represents

(i) hydrogen, halogen, lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by substituted amino, by lower alkoxy-carbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, or by substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy,  $C_3$ - $C_8$ -cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxy-carbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from  $-CH(OH)-R$ ,  $-CO-R$ ,  $-NR_1-CO-O-R$ ,  $-NR_1-CO-R$ ,  $-NR_1-CO-NR_1-R$ ,  $-NR_1-SO_2-R$ ,  $-NR_1-SO_2-NR_1-R$ ,  $-SO_2-R$ ,  $-SO_2-NR_1-R$ , or  $-SO_2-NR_1-CO-R$ , [R being as defined below and  $R_1$  being as defined above, or the group  $-N(R)(R_1)$  represents amino which is disubstituted by lower alkylene {which may be interrupted by O,  $S(O)_n$  or  $NR_0$ } or which is disubstituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

$X_1$  represents  $C_3$ - $C_8$ -cycloalkylene,  $C_3$ - $C_8$ -cycloalkenylene,  $C_3$ - $C_8$ -cycloalkylidene, oxo- $C_3$ - $C_8$ -cycloalkylene, oxo- $C_3$ - $C_8$ -cycloalkenylene, or oxo- $C_3$ - $C_8$ -cycloalkylidene;

$X_2$  represents  $-O-$ ,  $-S(O)_n-$  or a group of the formula  $-N(R_4)-$ ;

$R_3$  and  $R_4$ , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl,  $C_3$ - $C_8$ -cycloalkyl,  $C_3$ - $C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, substituted carbamoyl, and  $-S(O)_n-R$ ;

$R_3$  and  $R_4$  together represent lower alkylene [which may be interrupted by O,  $S(O)_n$ , or  $NR_0$ ] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl,  $C_3-C_8$ -cycloalkyl,  $C_3-C_8$ -cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy,  $C_3-C_8$ -cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, is derived from phenyl, naphthyl or pyridyl;

wherein, in each case, the amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by  $C_3-C_8$ -cycloalkyl, by  $C_3-C_8$ -cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O,  $S(O)_n$  or  $NR_0$ ] or is di-substituted by lower alkylene which is condensed at two adjacent

carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by  $-\text{CO}-(\text{O})_v-\text{R}$  and the integer  $v$  is 0 or 1;

wherein, in each case, the integer  $n$  is 0, 1 or 2;

wherein, in each case,  $\text{R}_0$  represents hydrogen or lower alkyl;

wherein, in each case,  $\text{R}$  represents hydrogen, lower alkyl,  $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ , (carbocyclic or heterocyclic) aryl-lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

4. A compound according to claim 1 of formula (I) or a salt or a tautomer thereof in which  $\text{alk}_1$  and  $\text{alk}_2$ , independently of one another, represent a single bond or lower alkylene;

$\text{R}_1$  represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

$\text{R}_2$  represents

(i) hydrogen;

(ii) amino, amino which is monosubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkyl or by  $\text{C}_2\text{-C}_6\text{-alkylene}$  or amino which is monosubstituted by  $-\text{CO}-\text{O}-\text{R}$  and  $\text{R}$  being lower alkyl;

(iii) lower alkoxy-carbonyl-oxy or (carbocyclic or heterocyclic) aryl-carbonyl-oxy;

(vi) a group selected from  $-\text{CH}(\text{OH})-\text{R}$  and  $\text{R}$  being hydrogen, lower alkyl or phenyl-lower alkyl,  $-\text{CO}-\text{R}$  and  $\text{R}$  being hydrogen or lower alkyl,  $-\text{NR}_1-\text{CO}-\text{O}-\text{R}$  and  $\text{R}_1$  being hydrogen and  $\text{R}$  being lower alkyl,  $-\text{NR}_1-\text{CO}-\text{R}$  and  $\text{R}_1$  being hydrogen or lower alkyl and  $\text{R}$  being lower alkyl, phenyl or lower alkoxy-lower alkyl,  $-\text{NR}_1-\text{SO}_2-\text{R}$  and  $\text{R}_1$  being hydrogen or lower alkyl and  $\text{R}$  being lower alkyl, phenyl-lower alkyl, phenyl or naphthyl,  $-\text{NR}_1-\text{SO}_2-\text{NR}_1-\text{R}$  and  $\text{R}_1$  being hydrogen and  $-\text{N}(\text{R}_1)(\text{R})$  being amino disubstituted by lower alkyl or by  $\text{C}_2\text{-C}_6\text{-alkylene}$  or being morpholino, piperazino or 4-lower alkyl-piperazino,  $-\text{SO}_2-\text{R}$  and  $\text{R}$  being lower alkyl or phenyl;

$\text{X}_1$  represents  $\text{C}_3\text{-C}_8\text{-cycloalkylene}$ ;

$\text{X}_2$  represents  $-\text{O}-$  and  $\text{R}_3$  is hydrogen; or

$\text{X}_2$  represents a group of the formula  $-\text{N}(\text{R}_4)-$  and  $\text{R}_4$  is hydrogen or lower alkyl; and

$\text{R}_3$  represents

(i) hydrogen, lower alkyl,  $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ ,  $\text{C}_3\text{-C}_8\text{-cycloalkyl-lower alkyl}$ , or phenyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: hydroxy, lower alkoxy, hydroxy-lower alkoxy, amino, amino monosubstituted by lower alkoxy-carbonyl or disubstituted by lower alkyl, morpholino, piperazino, 4-lower alkyl-piperazino, 4-lower alkoxy-carbonyl-piperazino and carbamoyl disubstituted by lower alkyl; or

$X_2$  and  $R_3$  together represent morpholino or 4-lower alkyl-piperazino;

wherein, in each case, any aryl moiety as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, nitro, lower alkyl, phenyl, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy and lower alkoxycarbonyl.

5. A compound according to claim 1 of formula (I) or a salt or a tautomer thereof in which  $alk_1$  and  $alk_2$ , independently of one another, represent a single bond or  $C_1$ - $C_3$ -alkylene;

$R_1$  represents hydrogen;

$R_2$  represents

hydrogen, lower alkoxycarbonyl-oxy, amino, amino di-substituted by  $C_3$ - $C_6$ -alkylene, a group selected from  $-NR_1-CO-R$  [ $R$  being lower alkyl, phenyl-lower alkyl, or phenyl and  $R_1$  being hydrogen],  $-NR_1-CO-O-R$  [ $R$  being lower alkyl],  $-NR_1-SO_2-R$  [ $R$  being lower alkyl, phenyl-lower alkyl, phenyl, naphthyl, or quinoliny] and  $R_1$  being hydrogen and phenyl being unsubstituted or substituted by lower alkyl, lower alkoxy, lower alkoxycarbonyl],  $-NR_1-SO_2-NR_1-R$  [ $R_1$  being hydrogen, and the group  $-N(R)(R_1)$  being di-lower alkylamino],  $-SO_2-R$  [ $R$  being lower alkyl], or  $-SO_2-NR_1-R$ , [ $R$  and  $R_1$  being each lower alkyl];

$X_1$  represents  $C_3$ - $C_6$ -cycloalkylene;

$X_2$  represents O and  $R_3$  represents hydrogen; or

$X_2$  represents a group of the formula  $-N(R_4)-$ ; and

$R_3$  represents hydrogen, lower alkyl, or phenyl which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

$R_4$  represents hydrogen;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen or lower alkoxy.

6. A compound according to claim 1 of formula (I) or a salt or a tautomer thereof in which  $alk_1$  and  $alk_2$  independently of one another, represent a single bond or methylene;

$R_1$  is hydrogen;

$X_1$  is 1,4-cyclohexylene;

$X_2$  is  $-O-$ ;  $R_2$  is  $-NH-SO_2-R$  and  $R$  being naphthyl; and  $R_3$  is hydrogen; or

$X_2$  is  $-NH-$ ;

$R_2$  represents  $-NH-SO_2-R$  and  $R$  is phenyl substituted by halogen, especially 4-chloro-phenyl, or naphthyl; and  $R_3$  represents hydrogen,  $C_1-C_4$ -alkyl which substituted by  $C_1-C_4$ -alkyl-amino or by  $C_1-C_4$ -alkyl-amino-carbonyl or by  $C_5-C_5$ -alkylene; or

$R_2$  represents  $C_1-C_4$ -alkylamino,  $C_1-C_4$ -alkoxycarbonyl-amino, such as tert-butoxycarbonyl-amino,  $-NH-SO_2-R$  and  $R$  being phenyl substituted by  $C_1-C_4$ -alkyl, or  $C_1-C_4$ -alkyl, or is  $NH-SO_2-N(R_1)(R)$  and  $R_1$  and  $R$  each being  $C_1-C_4$ -alkyl; and  $R_3$  represents hydrogen, phenyl or phenyl which is substituted by halogen; wherein the benzo ring  $A$  is unsubstituted or substituted by  $C_1-C_4$ -alkoxy.

7. A compound according to claim 1 of formula (I) or a salt thereof in which  $alk_1$  and  $alk_2$  independently of one another, represent a single bond or methylene;

$R_1$  is hydrogen;

$X_1$  is 1,4-cyclohexylene;

$X_2$  is  $-O-$ ;  $R_2$  is  $-NH-SO_2-R$  and  $R$  being naphthyl; and  $R_3$  is hydrogen; or

$X_2$  is  $-NH-$ ;

$R_2$  represents  $-NH-SO_2-R$  and  $R$  is phenyl substituted by halogen, especially 4-chloro-phenyl, or naphthyl; and  $R_3$  represents hydrogen,  $C_1-C_4$ -alkyl which substituted by  $C_1-C_4$ -alkyl-amino or by  $C_1-C_4$ -alkyl-amino-carbonyl or by  $C_5-C_5$ -alkylene; or

$R_2$  represents  $C_1-C_4$ -alkylamino,  $C_1-C_4$ -alkoxycarbonyl-amino,  $-NH-SO_2-R$  and  $R$  being phenyl substituted by  $C_1-C_4$ -alkyl, or  $C_1-C_4$ -alkyl, or is  $NH-SO_2-N(R_1)(R)$  and  $R_1$  and  $R$  each being  $C_1-C_4$ -alkyl; and  $R_3$  represents hydrogen, phenyl or phenyl which is substituted by halogen;

wherein the benzo ring  $A$  is unsubstituted or substituted by  $C_1-C_4$ -alkoxy.

8. A compound according to claim 1 of formula (I) or a pharmaceutically acceptable salt or a tautomer thereof consisting of the group selected from:

2-Cyclohexylamino-4-phenylamino-quinazoline;

cis/trans-2-(4-Piperidin-1-yl-cyclohexylamino)-4-phenylamino-quinazoline;

2-Cyclohexylamino-8-methoxy-4-phenylamino-quinazoline;

trans-2-(4-Acetoxy-cyclohexylamino)-4-phenylamino-quinazoline;

trans-Naphthalene-1-sulfonic acid [4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide;

trans-Naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-yl-amino)-cyclohexylmethyl]-amide;

trans-[4-(4-Phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester;

trans-4-(Aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline;

trans-[4-(4-Phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-methanesulfonamide;

trans-4-Methyl-N-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-benzenesulfonamide;

trans-3-[[4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-sulfamoyl]-4-methoxy-benzoic acid methyl ester;

trans-N-[4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-benzenesulfonamide;

trans-Naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

trans-N-[4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-methanesulfonamide;

trans-N-[4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-phenylmethanesulfonamide;

trans-N-[4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-4-tert-butylbenzenesulfonamide;

trans-N-[4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-2,4,6-trimethylbenzenesulfonamide;

trans-N-[4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-4-methylbenzenesulfonamide;

trans-N-[4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-benzamide;

trans-N-[4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-2-phenylacetamide;

trans-N,N-Dimethylamino sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

trans-Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

trans-[Naphthalene-1-sulfonic acid 4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl]-amide;

trans-Naphthalene-1-sulfonic acid {4-[(4-amino-6-bromo-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

trans-Naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

trans-Naphthalene-1-sulfonic acid {4-[(4-oxo-3,4-dihydro-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[(4-phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[(4-tert-butylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

(R,S)-cis-Naphthalene-1-sulfonic acid {3-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-(4-amino-quinazolin-2-ylamino)-cyclohexylethyl}-amide;

*trans*-Propane-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-fluorobenzenesulfonamide;

*trans*-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-nitrobenzenesulfonamide;

*trans*-Piperidine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Morpholine-4-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-2-sulfonic acid {4-[[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-hydroxy-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(3-methoxy-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-[2-(2-hydroxy-ethoxy)-ethylamino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[(4-methylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[(4-morpholin-4-yl-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(4-methyl-piperazin-1-yl)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-N,N-Dimethyl-2-{2-[[4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl]-amino]-quinazolin-4-ylamino}-acetamide;

*trans*-N,N-Dimethyl-2-{2-[[4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl]-amino]-quinazolin-4-ylamino}-acetamide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-piperidin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-morpholin-4-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-2-sulfonic acid {4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-diethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-dimethylamino-1,1-dimethyl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-[2-(4-methyl-piperazin-1-yl)-ethylamino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Propane-2-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-4-Methyl-piperazine-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-N-{4-[[4-(3-Diethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-C-phenylmethanesulfonamide;



*trans*-Naphthalene-2-sulfonic acid {4-[[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-N-{4-[[4-(3-Dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-4-fluoro-benzenesulfonamide;

*trans*-N(4)-(3-Dimethylamino-propyl)-N(2)-{4-[(2-methoxy-benzylamino)-methyl]-cyclohexylmethyl}-quinazoline-2,4-diamine;

*trans*-{2-{2-[[4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl]-amino}quinazolin-4-ylamino)-ethyl}-carbamic acid *tert*-butyl ester;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-amino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-4-{2-{2-[[4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl]-amino}-quinazolin-4-ylamino)-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-piperazin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-[(2-dimethylamino-ethyl)-methyl-amino]-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-amino-quinazolin-2-yl]-methyl-amino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-amino-6-fluoro-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-amino-6-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-amino-5-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-dimethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(2-diethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[[4-(3-diethylamino-propylamino)-8-methoxy-quinazolin-2-ylamino]-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methyl-amide;

*trans*-Naphthalene-1-sulfonic acid methyl-{4-[4-phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[1-(4-amino-quinazolin-2-ylamino)-1-methyl-ethyl]cyclohexylmethyl}-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[1-methyl-1-(4-phenylamino-quinazolin-2-ylamino)-ethyl]-cyclohexylmethyl}-amide;

*trans* Naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide;

*trans* Naphthalene-2-sulfonic acid (4-[[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-methyl]-cyclohexyl)-amide;

*trans* Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide;

*trans*-Naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide;

*trans*-Naphthalene-1-sulfonic acid (4-[[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-methyl]-cyclohexyl)-amide;

*trans*-Naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide;

*trans* Naphthalene-2-sulfonic acid (4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexyl)-amide;

*trans* Naphthalene-1-sulfonic acid (4-[[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl]-cyclohexyl)-amide;

*trans*-N-{4-[(4-Phenylamino-quinazolin-2-ylamino)]-cyclohexylmethyl}-(N,N-dimethylamino)-sulfonamide;

*trans*-N-(4-[[4-(4-Chloro-phenyl)amino]-quinazolin-2-ylamino]-cyclohexylmethyl)-(N,N-dimethylamino)-sulfonamide;

*trans*-N-(4-[[4-(4-Fluoro-phenyl)amino]-8-methoxy-quinazolin-2-ylamino]-cyclohexylmethyl)-(N,N-dimethylamino)-sulfonamide;

*trans*-N-{4-[4-(Cyclopropylmethylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-methanesulfonamide;

*trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester;

*trans*-{4-[4-(Cyclopropylamino)-8-methoxy-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester;

*trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-acetamide;

*trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-benzamide;

*trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-2-methoxy-benzamide;

*N-trans*-{4-[4-(Cyclopropylmethylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-2-methoxy-benzamide;

*trans*-4-(4-Chloro-phenylamino)-2-(4-methylaminomethyl-cyclohexyl)-quinazoline-2,4-diamine;

*trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-*N*-methyl-acetamide;

*trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-*N*-methyl-benzamide;

*trans*-2-Methoxy-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide;

*trans*-2-Methoxy-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide;

*trans*-{4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl}-carbamic acid *tert*-butyl ester;

*trans*-{4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl}-methanesulfonamide;

*trans*-{4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl}-(*N,N*-dimethylamino)-sulfonamide;

*trans*-4-(Cyclopropylmethyl)-2-(4-piperidin-1-ylmethyl-cyclohexyl)-quinazoline-2,4-diamine;

4-(3-Chloro-phenyl)-2-cyclohexyl-quinazoline-2,4-diamine; 4-(3-Chloro-phenyl)-2-cyclohexyl-quinazoline-2,4-diamine;

2-(*N*-Methyl-cyclohexylamino)-4-phenylamino-quinazoline;

2-(*N*-Methyl-cyclohexylamino)-8-hydroxy-4-phenylamino-quinazoline;

2-(*N*-Methyl-cyclohexylamino)-8-methoxy-4-phenylamino-quinazoline;

2-(*N*-Methyl-cyclohexylamino)-8-(methoxycarbonyl-methoxy)-4-phenylamino-quinazoline;

2-(*N*-Ethyl-cyclohexylamino)-8-hydroxy-4-(4-chloro-phenylamino)-quinazoline;

*trans*-2-(4-Benzoyloxy-cyclohexylamino)-4-phenylamino-quinazoline;

*trans*-2-(4-Acetoxy-cyclohexylamino)-4-(4-methoxy-phenylamino)-quinazoline;

N(2)-(trans-4-Dimethylamino-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine;  
1-{trans-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-ol;  
1-{trans-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-one;  
{trans-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-phenyl-methanol;  
1-{trans-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-2-phenyl-ethanone;  
N(2)-(trans-4-Ethanesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine;  
N(2)-(trans-4-Benzenesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine;  
1-(trans-4-[[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-pentan-1-ol;  
1-(trans-4-[[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-pentan-1-one;  
1-(trans-4-[[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-2-phenyl-ethanone; and  
(trans-4-[[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl]-cyclohexyl)-phenyl-methanone; or, in each case, a salt thereof.

9. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof or a tautomer thereof according to claim 1 for the manufacture of a pharmaceutical composition for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype.

10. A method of treatment of disorders and diseases associated with NPY receptor subtype Y5 comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a tautomer thereof according to claim 1.

11. A pharmaceutical composition for the treatment of diseases or disorders associated with NPY Y5 receptor subtype comprising a therapeutically effective amount of a compound

of formula (I) or a pharmaceutically acceptable salt or a tautomer thereof according to claim 1.

12. A pharmaceutical composition according to claim 11 for the treatment of disorders or disease states caused by eating disorders, of obesity, bulimia nervosa, diabetes, dyslipidimia, hypertension, memory loss, epileptic seizures, migraine, sleep disturbance, pain, sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion or diarrhea.



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<p>(21) International Application Number: PCT/EP96/05067</p> <p>(22) International Filing Date: 18 November 1996 (18.11.96)</p> <p>(30) Priority Data: 08/566,378 1 December 1995 (01.12.95) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 08/566,378 (CIP) Filed on 1 December 1995 (01.12.95)</p> <p>(71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basle (CH).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): RÜEGER, Heinrich [CH/CH]; Alemannenweg 6, CH-4112 Flüh (CH). SCHMIDLIN, Tibur [CH/CH]; Friedensgasse 36, CH-4056 Basle (CH). RIGOLLIER, Pascal [FR/FR]; 2, rue Sainte-Catherine, F-68100 Mulhouse (FR). YAMAGUCHI, Yasuchika [JP/CH]; Tellstrasse 44/2, CH-4053 Basle (CH). TINTELNOT-BLOMLEY, Marina [DE/DE]; Röttlerstrasse 1, D-79689 Maulburg (DE). SCHILLING, Walter [CH/CH]; Im Muspenacker, CH-4204 Himmelried (CH). CRISCIONE,</p>	<p>Leoluca [IT/CH]; Kirchstrasse 15, CH-4313 Möhlin (CH). MAH, Robert [CA/CH]; Baslerstrasse 258, CH-4123 Allschwil (CH).</p> <p>(74) Common Representative: NOVARTIS AG; Patent and Trade-mark Dept., Klybeckstrasse 141, CH-4002 Basle (CH).</p> <p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p> <p>(88) Date of publication of the international search report: 17 July 1997 (17.07.97)</p>	
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<div style="text-align: center;"> <p>(I)</p> </div>		
<p>(57) Abstract</p> <p>The invention relates to a compound of formula (I) in which the variables are as defined and/or a salt or a tautomer thereof; and relates to a method of treatment of disorders or diseases associated with NPY receptor subtype Y5, to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and to the manufacture of the compounds of formula (I) or a salt thereof.</p>		

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/05067

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D239/95 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 287 341 A (HESS ET. AL.) 1 September 1981 see example 18 ---	1-5
X	WO 92 07844 A (PFIZER INC.) 14 May 1992 see claims; example 85 ---	1-3
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 6, June 1993, WASHINGTON DC, US, pages 690-8, XP000652149 D. GIARDINA ET. AL.: "Structure-Activity Relationships in Prazosin-Related Compounds. 2. Role of the Piperazine Ring on alpha-Blocking Activity. " see table 1. --- -/--	1-5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

6 May 1997

Date of mailing of the international search report

30.05.97

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 96/05067

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 2, February 1981, WASHINGTON DC, US, pages 127-40, XP000653661 E. F. ELSLAGER ET. AL.: "Synthesis and Antimalarial Effects of N2-Aryl-N4-[(dialkylamino)alkyl]- and N4-Aryl-N2-[(dialkylamino)alkyl]- 2,4-quinazolinediamines." see tables I-IV	1-5
A	--- EP 0 614 911 A (ELF SANOFI) 14 September 1994 see whole document	1-12
A	--- EP 0 448 765 A (HEUMANN PHARMA GMBH) 2 October 1991 see whole document	1-12
P,A	--- WO 96 12489 A (ELI LILLY & CO.) 2 May 1996 see claims; examples -----	1-12

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/05067

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 10  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☒ Claims Nos.: 1-7, 9-12  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:  
Due to the very broad scope of the claims and the inclusion of vague  
definitions such as "heteroaryl", the search has been limited to the  
scope covered by the examples (Guidelines B-III, 3.7).
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

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Internat. Application No

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